Plasma alpha-tocopherol concentrations, raised fourfold by supplementation, fell by 70% after the operation in the supplemented group and to negligible levels in the placebo group. There were no significant differences between the groups with respect to release of creatine kinase MB isoenzyme over 72 hours, nor in the reduction of the myocardial perfusion defect determined by thallium 201 uptake. Electrocardiography provided no evidence of a benefit from antioxidant supplementation. Thus the supplementation regimen **prevented** the depletion of the primary lipid soluble antioxidant in plasma, but provided no measurable reduction in myocardial injury after the operation.

L85 ANSWER 38 OF 93 CAPLUS COPYRIGHT 2003 ACS
1997:665597 Document No. 127:326223 Clinical observation of Jinado in **treatment** of ischemic cerebrovascular disease. Mai, Jue; Chen, Liying (Department of Medicine, Guangning People's Hospital, Guangning, 526300, Peop. Rep. China). Guangdong Yixue, 18(8), 571-572 (Chinese) 1997. CODEN: GUYIEG. ISSN: 1001-9448. Publisher: Guangdongsheng Yixue Qingbao Yanjiuso.
AB Jinado, a German product of ginkgo leaf ext., contg. **flavonoid,** glycolaldehyde, and ginkgo esters, which improves the blood flow of the **ischemia tissues,** were tested in 50 inpatients with ischemic cerebrovascular disease. The total effective rate was 96%, the improvement rate of hemiplegia was 69%.

L85 ANSWER 39 OF 93 MEDLINE
97344378 Document Number: 97344378. PubMed ID: 9200825. The efficacy of antioxidants administered during low temperature storage of warm ischemic kidney tissue slices. McAnulty J F; Huang X Q. (Department of Surgical Sciences, School of Veterinary Medicine, University of Wisconsin, Madison 53706, USA.) CRYOBIOLOGY, (1997 Jun) 34 (4) 406-15. Journal code: 0006252. ISSN: 0011-2240. Pub. country: United States. Language: English.
AB Accumulation of products of lipid peroxidation (malondialdehyde, conjugated dienes, lipid peroxides, and Schiff bases) was evaluated in rabbit kidney cortex slices made ischemic for 60 min followed by 18 h storage at 5 degrees C in UW Na gluconate solution and 210 min normothermic reoxygenated incubation. In addition, the effect of adding Trolox (1 mM), deferoxamine (1 mM), and ascorbate (1 mM) as supplemental antioxidants to the UW gluconate solution was evaluated. Lipid peroxidation was slightly increased after hypothermic storage compared to slices subjected to ischemia alone but was not significantly different than ischemic slices during subsequent incubation at normothermia. The addition of either deferoxamine or Trolox to the storage solution substantially reduced lipid peroxidation both during hypothermic storage and subsequent to normothermic incubation. Ascorbate had a mild prooxidant effect as a sole additive to the UW gluconate solution but was clearly prooxidant when combined with either deferoxamine or Trolox. These results suggest that supplemental antioxidants added to the UW gluconate solution under conditions analogous to machine perfusion preservation have a potential role in reducing oxidative stress in kidney **tissues** harvested after warm **ischemia** and that hypothermia may be a valuable adjunct to resuscitative **therapeutic** regimens developed for salvage of ischemic kidneys for transplantation.

L85 ANSWER 40 OF 93 MEDLINE DUPLICATE 12
1998011557 Document Number: 98011557. PubMed ID: 9350470. Antioxidative vitamins in **prevention** of ischemia/reperfusion injury. Nagel E; Meyer zu Vilsendorf A; Bartels M; Pichlmayr R. (Department of Abdominal and Transplantation Surgery, Hannover Medical School, Germany.) INTERNATIONAL JOURNAL FOR VITAMIN AND NUTRITION RESEARCH, (1997) 67 (5) 298-306. Ref: 56. Journal code: 1273304. ISSN: 0300-9831. Pub. country:

Searched by: Mary Hale 308-4258 CM-1 1E01

Switzerland. Language: English.

AB Involvement of oxygen free radicals in ischemia-/reperfusion injury is based on measurement of increased products of lipid peroxidation after organ ischemia and restoration of blood flow during surgical operations and reperfusion of organ transplants. In cardiology inverse epidemiological correlations between plasma **vitamin E** levels and mortality due to ischemic heart disease, as well as beneficial effects of **vitamin E** on experimentally induced oxidative damage to the heart support the hypothesis, that **vitamin E** might have a protective role against myocardial ischemia-/reperfusion injury. In abdominal surgery efficiency of free radical scavengers has been intensively studied on animal models of hepatic ischemia and reperfusion. Examination of free radical scavengers and adenosine **metabolites** in liver **tissue** during hepatic **ischemia** revealed that **vitamin E** and glutathione levels as well as hepatic adenosine triphosphate levels are decreased during hepatic ischemia and reperfusion. The beneficial effects of alpha-tocopherol on hepatic viability and survival rate after ischemia and reperfusion demonstrated in these studies will be of great importance concerning further studies in organ preservation. In clinical kidney transplantation **prevention** of lipid peroxidation and improvement in kidney viability and function was demonstrated after infusion of a multivitamin cocktail in a prospective randomised study.

L85 ANSWER 41 OF 93 MEDLINE DUPLICATE 13

97414746 Document Number: 97414746. PubMed ID: 9269412. Activation of tyrosine hydroxylase in striatum of newborn piglets in response to hypocapnic ischemia and recovery. Pastuszko P; Wilson D F. (Department of Biochemistry and Biophysics Medical School, University of Pennsylvania, Philadelphia 19104, USA.) ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1997) 411 65-73. Journal code: 0121103. ISSN: 0065-2598. Pub. country: United States. Language: English.

AB The present study describes the effect of hypocapnic ischemia caused by hyperventilation on striatal levels of dopamine, DOPAC, HVA and activity of tyrosine hydroxylase in striatal synaptosomes isolated from the brain of newborn piglets. Hyperventilation did not result in statistically significant changes in the striatal level of dopamine and its major **metabolites**; however, it was observed that after 20 min of recovery the levels of striatal tissue dopamine, DOPAC and HVA increase by 195%, 110% and 205%, respectively. The level of DOPA (3,4-dihydroxyphenylalanine), which was used as an index of tyrosine hydroxylase activity, also increased after recovery. The rate of dopamine synthesis was 32 pmoles/mg protein/10 min in control piglets and after recovery this increased to 132 pmoles/mg protein/10 min. Measurement of the tyrosine hydroxylase activity in Triton X-100 **treated** synaptosomes showed that, after 20 min of recovery, there was an increase in Vmax with no change in K(m) for pteridine cofactor, compared to control. This is consistent with the enzyme having been covalently modified (activated) during **tissue ischemia** caused by hyperventilation and remaining activated well into the recovery period. We postulate that ischemia can induce long lasting alterations in dopamine synthesis, which may play some role in mediation of hypoxic cell injury in immature brain.

L85 ANSWER 42 OF 93 MEDLINE

97478842 Document Number: 97478842. PubMed ID: 9412018. [The membrane phospholipid peroxidation and Ca-dependent ATPase activity of the microsomal fractions isolated from rat renal **tissue** in thermal **ischemia** with and without alpha-tocopherol protection]. Perekisnoe okislenie membrannykh fosfolipidov i Ca-zavisimaia ATFaznaia

Searched by: Mary Hale 308-4258 CM-1 1E01

aktivnost' mikrosomnykh fraktsii, vydelennykh iz pochechnoi tkani krys pri teplovoi ishemii bez protektsii i s protektsiei al'fa-tokoferolom. Golod E A. UROLOGIIA I NEFROLOGIIA, (1997 Sep-Oct) (5) 5-9. Journal code: 0032352. ISSN: 0042-1154. Pub. country: RUSSIA: Russian Federation. Language: Russian.

AB The author studied the effects of 30-min heat ischemia of rat kidneys on the level of malonic dialdehyde (MDA) and Ca-dependent ATPase activity of microsomal fraction isolated from the cortical substance in the presence and absence of antibiotic alameticine and ortovandate in the incubation medium and protective action on Ca-ATPase activity of rat pretreatment with alpha-tocopherol (TP). It has been demonstrated that thermal ischemia induces inhibition of Ca-ATPase activity of microsomes resistant to vanadate. Administration of TP reduced MDA level, enhanced Ca-ATPase microsomal activity in the presence of alameticine against inhibition of enzymic activity in the absence of alameticine. This indicates a rise in the true enzyme activity under decreasing membrane permeability in conditions of diminishing activity of lipid peroxidation in response to TP effects.

L85 ANSWER 43 OF 93 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

96012142 EMBASE Document No.: 1996012142. Effect of **vitamin e** on hydrogen peroxide production by human vascular endothelial cells after hypoxia/reoxygenation. Martin A.; Zulueta J.; Hassoun P.; Blumberg J.B.; Meydani M.. JMUSDAHNRCA, Tufts University, 711 Washington Street,Boston, MA 02111, United States. Free Radical Biology and Medicine 20/1 (99-105) 1996.
ISSN: 0891-5849. CODEN: FRBMEH. Pub. Country: United States. Language: English. Summary Language: English.

AB Changes in oxidative stress status play an important role in **tissue** injury associated with **ischemia**-reperfusion events such as those that occur during stroke and myocardial infarction. Endothelial cells (EC) from human saphenous vein and aorta were incubated for 22 h and found to take up **vitamin E** from media containing 0-60 mM **vitamin E** in a dose-dependent manner. EC supplemented with 23 or 28 mM **vitamin E** in the media for 22 h were maintained at normoxia (20% O2, 5% CO2, and balance N2) or exposed to hypoxic conditions (3% O, 5% CO2, and balance N2) for 12 h, followed by reoxygenation (20% O2) for 30 min. Saphenous EC supplemented with 23 mM **vitamin E** produced less ($p < 0.05$) H2O2 than unsupplemented controls, both at normoxic condition (supplemented: 4.9 .+-. 0.05 vs. control: 10.9 .+-. 1.3 pmol/min/106 cells) and following hypoxia/reoxygenation (supplemented: 6.4 .+-. 0.78 vs. control: 17.0 .+-. 2.7 nmol/min/106 cells). In contrast, aortic EC, which were found to have higher superoxide dismutase and catalase activity than EC from saphenous vein, did not produce any detectable levels of H2O2. Following hypoxia/reoxygenation, the concentration of **vitamin E** in supplemented saphenous EC was 62% lower than cells maintained at normoxia (0.19 .+-. 0.03 vs. 0.5 .+-. 0.12 nmoles/106 cells. $p < 0.001$); in aortic EC **vitamin E** content was reduced by 18% following reoxygenation (0.86 .+-. 0.16 vs, 070 .+-. 0.09 nmoles/106 cells, $p < 0.05$). Therefore, enrichment of **vitamin E** in EC decreases H2O2 production and thus may reduce the injury associated with ischemia-reperfusion events.

L85 ANSWER 44 OF 93 MEDLINE

96318991 Document Number: 96318991. PubMed ID: 8734301. Pathogenic mechanisms in familial amyotrophic lateral sclerosis due to mutation of Cu, Zn superoxide dismutase. Gurney M E; Cutting F B; Zhai P; Andrus P K; Hall E D. (Central Nervous System Diseases Research Unit, Upjohn Laboratories, Kalamazoo, MI 49001, USA.) PATHOLOGIE BIOLOGIE, (1996 Jan)

Searched by: Mary Hale 308-4258 CM-1 1E01

44 (1) 51-6. Ref: 38. Journal code: 0265365. ISSN: 0369-8114. Pub. country: France. Language: English.

AB Oxidative mechanisms of damage have been implicated indirectly in the damage to brain **tissue** caused acutely by **ischemia** or chronically by neurodegenerative diseases. A direct link between pathogenesis and antioxidant enzyme systems has come from studies of a genetic form of amyotrophic lateral sclerosis (ALS). ALS causes the degeneration of motor neurons in cortex, brainstem and spinal cord with consequent progressive paralysis and death. The disease occurs in both sporadic and familial forms. Some 20% of kindreds in which ALS is inherited in an autosomal dominant fashion have mutations in the gene (SOD1) encoding Cu, Zn superoxide dismutase (SOD). Several SOD1 mutations have been shown by ourselves and others to cause motor neuron disease when expressed at high levels in transgenic mice, whereas transgenic mice expressing comparable amounts of wild-type human SOD do not show clinical disease. Thus, we have argued that motor neuron disease is caused by gain-of-function mutations in the human SOD1 gene. Our current experiments investigate the link between mutation of SOD1 and oxidative pathways of damage.

L85 ANSWER 45 OF 93 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

95271779 EMBASE Document No.: 1995271779. Enhanced vulnerability to secondary ischemic insults after experimental traumatic brain injury. DeWitt D.S.; Jenkins L.W.; Prough D.S.. Department of Anesthesiology, University of Texas Medical Branch,Galveston, TX 77555-0591, United States. New Horizons: Science and Practice of Acute Medicine 3/3 (376-383) 1995. ISSN: 1063-7389. CODEN: NEHOFH. Pub. Country: United States. Language: English. Summary Language: English.

AB Both experimental traumatic brain injury and clinical traumatic brain injury appear to render the brain more vulnerable to a second ischemic insult. The mechanisms of enhanced vulnerability to subsequent ischemia appear to include a reduced ability to increase cerebral blood flow in response to hypotension, hypoxemia, or acute anemia and increased **tissue** sensitivity to **ischemia**. Although numerous mediators may be involved in increased tissue sensitivity, those that particularly merit investigation include oxygen free radicals, glutamate, arachidonate **metabolites**, calcium ions, and protein kinase C.

L85 ANSWER 46 OF 93 CAPLUS COPYRIGHT 2003 ACS

1996:41117 Document No. 124:135649 Evaluation of the antioxidant properties of the angiotensin-converting enzyme inhibitor, captopril and the nucleotide enhancing agent, acadesine. Wasil, M.; Kelly, F. J. (Rayne Institute, St Thomas' Hospital Medical School, London, SE1 7EH, UK). Redox Report, 1(5), 361-7 (English) 1995. CODEN: RDRPE4. ISSN: 1351-0002. Publisher: Churchill Livingstone.

AB The angiotensin-converting enzyme inhibitor, captopril and the nucleotide enhancing agent, acadesine, protect myocardial **tissue** from **ischemia**/reperfusion-induced injury. Although both drugs have well established, independent mechanisms of cardiac protection, they may also have antioxidant activity which could contribute to their beneficial action. In this study the authors have examd. the antioxidant activity of captopril and acadesine by examg. their ability to scavenge ABTS radicals, formed from the interaction of ferryl metmyoglobin with phenothiazine in the presence of hydrogen peroxide. For comparison, the authors compared these results to those obtained for a range of other drugs commonly used for the **treatment** of cardiovascular disorders. These included verapamil (arrhythmia), isosorbide dinitrate (angina), atenolol (hypertension) and enalapril (congestive heart failure). The antioxidant properties of these drugs were then compared to the well characterized antioxidants, Trolox (a water sol. **vitamin E** analog),

Searched by: Mary Hale 308-4258 CM-1 1E01

ascorbate and glutathione. Captopril and acadesine were both shown to be efficient scavengers of ABTS radicals, importantly at drug concns. expected to be found in vivo. These data confirm that the antioxidant potential of captopril and acadesine may be an important component of their mechanism of action, with both drugs probably protecting the myocardium against oxygen derived free radicals during ischemia/reperfusion.

L85 ANSWER 47 OF 93 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
1996:25656 Document No.: PREV199698597791. Oxidants and antioxidants in clinical medicine: Past, present and future potential. Bland, Jeffrey S.. HealthComm Intl. Inc., Clin. Res. Cent., PO Box 1729, 5800 Soundview Drive, Build. B, Gig Harbor, WA 98335 USA. Journal of Nutritional & Environmental Medicine (Abingdon), (1995) Vol. 5, No. 3, pp. 255-280. ISSN: 1359-0847. Language: English.

AB This article reviews aspects of past, present and future potential of oxidants and antioxidants in clinical medicine. Beginning with the observation that antioxidants help to defend against cellular lipid peroxidation and lipofuscin and ceroid pigment formation, the review moves to epidemiological and clinical intervention information that specifies the molecular mode of action of various antioxidants in helping to defend against oxidative stress. This discussion is presented in the context of free radical pathology and its relationship to reactive oxygen species and the interrelationship of these processes to free radical chain termination mediated by enzyme and small molecule antioxidants. Accumulating medical and scientific literature in this area indicates that many clinical problems in medicine, both chronic and acute, are related to the maintenance of the intracellular redox potential. This review details new methods of assessing oxidative stress, evaluating need for specific antioxidant **therapy** and following the progress of intervention utilizing markers of redox potential in the patient. The emphasis is on development of a new, comprehensive model for viewing oxidants and antioxidants in a clinical context, and on the management of antioxidant disorders using a series of redox reagents derived from specific foods which yield high concentrations of **vitamin E**, vitamin C, **flavonoids**, carotenes, polyphenols and quinoids.

L85 ANSWER 48 OF 93 MEDLINE DUPLICATE 14
95088952 Document Number: 95088952. PubMed ID: 7996477. Effects of an antistroke agent MCl-186 on cerebral arachidonate cascade. Watanabe T; Egawa M. (Pharmaceutical Laboratory, Yokohama Research Center, Mitsubishi Chemical Corporation, Japan.) JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1994 Dec) 271 (3) 1624-9. Journal code: 0376362. ISSN: 0022-3565. Pub. country: United States. Language: English.

AB Activation of the cerebral arachidonate (AA) cascade is one of the major causes of edema and **tissue** injury in cerebral **ischemia**, particularly after reperfusion. The cascade produces toxic oxygen radicals responsible for peroxidative neurodegeneration and synthesizes, the potent edematous inducer, leukotrienes. The present study was undertaken to evaluate the effect of MCl-186 (3-methyl-1-phenyl-pyrazolin-5-one), a radical scavenger and antioxidant which has beneficial anti-ischemic actions, on the cerebral AA cascade. Postischemic **treatment** with MCl-186 (1.0 and 3.0 mg/kg i.v.) significantly inhibited the aggravation of cortical edema seen 60 min after recirculation following 30 min of ischemia in gerbils. An antilipoxygenase agent, FPL-55712 (7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2- hydroxypropoxy]-4-oxo-8-propyl-4H-1-**benzopyran**-2-carboxylic acid, monosodium salt; 10 mg/kg i.v.) or AA-861 ((2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinon e; 60 mg/kg i.p.) was also effective in this model; however, indomethacin (4

Searched by: Mary Hale 308-4258 CM-1 1E01

mg/kg i.p.), a cyclooxygenase inhibitor, was ineffective. Concomitant **treatment** with MCl-186 (0.1-3.0 mg/kg i.v.) remarkably inhibited the swelling observed 24 hr after cortical infusion of AA (80 micrograms) in rats. Similarly, antilipoxygenase agents clearly inhibited the AA-induced edema. Furthermore, postischemic **treatment** with MCl-186 (0.3-3.0 mg/kg i.v.) inhibited the facilitation of cerebral leukotriene synthesis seen 15 min after recirculation following 30 min of ischemia in gerbils. These findings suggest that the site of action of MCl-186 as an anti-ischemic agent may be closely associated with the cerebral AA cascade, especially the lipoxygenase system, activated by ischemia-reperfusion.

L85 ANSWER 49 OF 93 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
94326631 EMBASE Document No.: 1994326631. The effect of amflutizole, a xanthine oxidase inhibitor, on ischemia-evoked purine release and free radical formation in the rat cerebral cortex. O'Regan M.H.; Smith-Barbour M.; Perkins L.M.; Cao X.; Phillis J.W.. Department of Physiology, School of Medicine, Wayne State University,Detroit, MI 48201, United States. Neuropharmacology 33/10 (1197-1201) 1994.
ISSN: 0028-3908. CODEN: NEPHBW. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB The efflux of hypoxanthine, xanthine and uric acid into cortical superfusates was studied with the cortical cup technique in the rat. Twenty minutes of four vessel occlusion followed by reperfusion results in a massive increase in the efflux of these purine **metabolites**. Amflutizole, 10 .mu.M administered topically into the cortical cups, enhanced the ischemia-evoked release of hypoxanthine while it suppressed xanthine formation. Uric acid levels were not affected. Amflutizole also eliminated the ischemia/reperfusion-evoked generation of free radical adducts of .alpha.-(4-pyridyl-1-oxide)-N-tert-butylnitrone (POBN) detected by electron spin resonance. These results are consistent with a block of xanthine oxidase by amflutizole and support the involvement of xanthine oxidase in free radical mediated **tissue** damage following **ischemia**/reperfusion.

L85 ANSWER 50 OF 93 MEDLINE
94285873 Document Number: 94285873. PubMed ID: 8015492. Antioxidant effectiveness in **ischemia**-reperfusion **tissue** injury.
Das D K; Maulik N. (Department of Surgery, University of Connecticut School of Medicine, Farmington 06030.) METHODS IN ENZYMOLOGY, (1994) 233 601-10. Ref: 65. Journal code: 0212271. ISSN: 0076-6879. Pub. country: United States. Language: English.
AB In summary, much evidence supports the formation of toxic oxygen **metabolites** in ischemic reperfused tissue. Tissues are equipped with both an intracellular and extracellular antioxidant defense system. The defense system can also be divided into enzymatic and nonenzymatic defenses. Important components of a nonenzymatic antioxidant include alpha-tocopherol, ascorbic acid, and beta-carotene as well as other compounds that can react with radicals to form less reactive products such as sulfur-containing amino acids. Extracellular fluid comprises a second line of defense against oxidant injury. These extracellular antioxidants include ceruloplasmin, albumin, transferrin, haptoglobin, and uric acid. The oxidant injury can potentially occur during ischemia and reperfusion due to (1) an excess production of oxygen free radicals, (2) a decrease in antioxidant defenses, or (3) both. Because antioxidants function by removing the toxic oxygen **metabolites**, they are generally highly effective in reducing ischemia-reperfusion injury.

L85 ANSWER 51 OF 93 MEDLINE
94123118 Document Number: 94123118. PubMed ID: 8293315. Effects of

alpha-tocopherol on lipid peroxidation and mitochondrial reduction of tetraphenyl tetrazolium in the rat brain. Villalobos M A; De La Cruz J P; Carrasco T; Smith-Agreda J M; Sanchez de la Cuesta F. (Department of Anatomy, School of Medicine, University of Malaga, Spain.) BRAIN RESEARCH BULLETIN, (1994) 33 (3) 313-8. Journal code: 7605818. ISSN: 0361-9230. Pub. country: United States. Language: English.

AB The antioxidant effect of alpha-tocopherol was assessed in a model of ischemia-reperfusion in the rat brain. In this model, permanent ischemia of the cortical branches of the middle cerebral artery was combined with bilateral occlusion of the common carotid arteries for 1 h and restoration of circulation for a period of 2 h. Lipid peroxidation and mitochondrial reduction of tetraphenyl tetrazolium (TPT) were determined in both untreated and d-alpha-tocopherol **treated** rats. Ferrous sulfate and ascorbic acid (FeAs) were used to induce lipid peroxidation via the formation of hydroxyl anions. Malondialdehyde (MDA) increased in the ischemia-reperfusion areas (+101%), but FeAs-induced MDA did not vary in the area of permanent ischemia. Brain **tissue** undergoing **ischemia**-reperfusion was about 50% less sensitive to the antioxidant effect of ascorbic acid. The reduction of TPT showed 52% mitochondrial damage in the area of ischemia-reperfusion, whereas mitochondrial activity in the area of permanent ischemia was 177 times lower as compared to controls. d-alpha-tocopherol caused a 40% inhibition of MDA production and 16.5% and 21.5% decrease in mitochondrial activity in the areas of ischemia-reperfusion and permanent ischemia, respectively.

L85 ANSWER 52 OF 93 JICST-EPlus COPYRIGHT 2003 JST

940178710 Nitric oxide and free radical scavengers protect intestinal mucosal damage induced by ischemia and reperfusion.. ICHIKAWA H. Kyoto Prefectural Univ. Medicine. Kyoto Furitsu Ika Daigaku Zasshi (Journal of Kyoto Prefectural University of Medicine). (1994) vol. 103, no. 1, pp. 141-161. Journal Code: Z0618A (Fig. 15, Ref. 58) CODEN: 0023-6012; Pub. Country: Japan. Language: English.

AB Oxygen-derived free radicals are putative mediators of **tissue** injury induced by **ischemia** and reperfusion. The roles of oxygen-derived free radicals, lipid peroxidation, the antioxidative defense mechanism and nitric oxide in the intestinal mucosal injury induced by ischemia-reperfusion were investigated in rats. Ischemia was induced by ligating the celiac artery and clamping the superior mesenteric artery for 30min. Reoxygenation was produced by removal of the clamp 60min after ischemia. Intra-luminal hemoglobin level significantly increased from mean basal level after 60min of reperfusion. This increase in intra-luminal hemoglobin level was significantly inhibited by pretreatment either with hSOD+catalase or with exogenous .ALPHA.-tocopherol. TBA-reactive substances in the intestinal mucosa, an index of lipid peroxidation, were also significantly higher than basal level after 60min of reperfusion. The .ALPHA.-tocopherol concentration in the intestinal mucosa decreased significantly with time after reperfusion following 30min of ischemia. The increase in TBA-reactive substances and the decrease in .ALPHA.-tocopherol in the intestinal mucosa after ischemia-reperfusion were inhibited by the pretreatment with hSOD and catalase. Allopurinol **treatment** significantly inhibited intestinal mucosal injury as well as the increase in lipid peroxidation in the intestinal mucosa. On the other hand, N5-nitro-L-arginine(L-NNA), a selective inhibitor of NO synthesis, inhibited the recovery of blood flow in the mucosa after removal of the vascular clamp, while SOD+catalase reversed the inhibition by L-NNA. Although the administration of L-NNA induced extensive damage to the intestine after ischemia-reperfusion, sodium nitroprusside(SNP) which spontaneously generates NO significantly attenuated the damage. (abridged author abst.)

Searched by: Mary Hale 308-4258 CM-1 1E01

L85 ANSWER 53 OF 93 CAPLUS COPYRIGHT 2003 ACS
1994:602345 Document No. 121:202345 **Vitamin E** levels in ischemic cerebrovascular diseases. Mungen, Bulent; Aksakal, Mesut; Akyol, Ali; Karakilcik, Ziya; Bulut, Serpil (Faculty Medicine, Firat University, Elazig, Turk.). Turkish Journal of Medical Sciences, 21(2), 103-5 (English) 1994. CODEN: TJMEEA. ISSN: 1300-0144.

AB Free radicals play an important role in tissue damage and cytolysis which occur in ischemic cerebrovascular diseases (CVDs). Formation of free radicals could be **prevented** by antioxidant substances. One of the potent antioxidant substances is **Vitamin E**. **Vitamin E prevents** formation of free radicals and stabilizes the cell membrane, thus reducing **tissue** damage due to **ischemia** by decreasing excessive calcium passage into the cell. In this study, we investigated whether there is a relationship between **vitamin E** levels and occurrence of ischemic CVDs. We obsd. that **vitamin E** levels were significantly lower($p < 0.005$) in patients with ischemic CVD (42 patients aged .gtoreq. 50 yr). It was concluded that low **vitamin E** levels may play a role in the occurrence of ischemic CVDs.

L85 ANSWER 54 OF 93 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
94008334 EMBASE [illegible] ...lar and thrombosis pathology ass... ...B440 Life Sciences Building, Mich... ...MI 48824, United States. Hematology/Onc... ...(1143-1151) 1993. ISSN: 0889-858... ...ed States. Language: English. Summa...

1/11/03 Obtain order

AB Although there... ...stroke, arrhythmia, myocardial inf... ...mortem examinations of cocaine abusers... ...ese pathologic changes are largely specula... ...some of the complicating factors from the clinical surveys of cardiovascular pathology in cocaine abusers is that most addicts abuse other pharmacologically active substances. Thus, the direct contribution of cocaine to observed pathologies is difficult to dissect from the effects of other compounds. Moreover, although cocaine has been shown to block sodium channels and uptake of amine neurotransmitters in blood vessels and platelets, direct association of cardiovascular pathologies to these mechanisms has not been demonstrated. The correlation of cocaine-induced arterial thrombosis, **tissue ischemia**, and myocarditis also has not been definitively linked to adrenergic mechanisms in humans. Thus, there is correlative evidence from autopsies and emergency rooms for vasospasm, thrombosis, and cardiac arrhythmia in cocaine abuse. Some studies in animals have shown increased reactivity of blood vessels and arrhythmias linked to cardiac ischemia. However, dispute continues over the etiology of cocaine- associated sudden cardiac death, especially in athletes; there is discussion of both irretrievable cardiac arrhythmia or sudden coronary vasospasm as the possible initiating factor in the sudden death of an otherwise apparently healthy individual. Additionally, the secondary mechanisms involved in some of the observed cardiovascular pathologies induced by cocaine have not been well characterized. Currently, acute cocaine intoxication symptoms are pharmacologically managed with anticonvulsants, the pan-alpha blocker regitine, antiarrhythmic compounds, nitrate vasodilators, or calcium entry blockers. Successful **treatment** of cocaine-associated myocardial infarctions with heparin and thrombolytics has recently been reported. Cautionary notes for the use of thrombolytics have also been raised in the **treatment** of myocardial infarctions in habitual cocaine abusers, owing to a possible increased tendency of these patients for intracranial bleeding and increased incidence of mycotic aneurysms. Additionally, the use of propranolol has been

Searched by: Mary Hale 308-4258 CM-1 1E01

questioned. Propranolol administered to volunteers taking cocaine increased coronary vascular resistance. Vargas et al have shown an unmasking of cocaine-induced contraction in porcine coronary arteries in the presence of propranolol. Beta-blockers and thrombolytic compounds should be used with caution in **treating** cardiovascular crises associated with cocaine use. Although pharmacologic intervention has decreased the acute mortality, often significant morbidity remains. Subchronic and chronic cocaine **treatment** studies in animals suggest that cocaine may produce stable functional changes in cardiovascular tissues that persist even in the absence of cocaine or cocaine **metabolites**. If the underlying mechanisms for the reactivity changes and cardiovascular pathology induced by cocaine were better understood, more effective **therapy** for recovering cocaine addicts could be developed. Additionally, in the cocaine-associated pathologies such as accelerated atherosclerosis and myocarditis, it is possible that cocaine may augment the pathologic processes that result in these conditions at older ages in non- cocaine users. Investigation of the mechanisms of cocaine-induced vascular reactivity and thrombosis may provide insight into idiopathic mechanisms of cardiovascular pathology.

L85 ANSWER 55 OF 93 CAPLUS COPYRIGHT 2003 ACS
1994:570200 Document No. 121:170200 The influence of 5-amino-4-imidazolecarboxamide ribonucleotide (AICAR) in reperfusion damage after intestinal ischemia. Schoenberg, M. H.; Poch, B.; Moch, D.; Beger, H. G. (Chir. Klin., Univ. Ulm, Ulm, W-7900, Germany). Chirurgisches Forum fuer Experimentelle und Klinische Forschung 417-22 (German) 1993. CODEN: CFEKA7. ISSN: 0303-6227.

AB A model was used of intestinal ischemia and reperfusion in 12 cats which were subjected to intestinal ischemia for 2 h and 1 h of reperfusion, resp. Six cats were **treated** with 5-amino-4-imidazolecarboxamide ribonucleotide (dosage: 2.5 mg/min kg-1 body wt.) as an continuous i.v. infusion. **Treatment** was started 30 min before ischemia lasting until 30 min after reperfusion. Before and 2 h after ischemia as well as 10 and 60 min after reperfusion, tissue samples were excised for measurement of the purine **metabolites** and myeloperoxidase. Moreover, the tissue samples were examd. histol. AICAR **treatment** led to an increase of adenosine concns. within the intestinal **tissue**, not only during **ischemia** but also during reperfusion. Consequently, these high adenosine concns. inhibited the accumulation of polymorphonuclear (PMN) leukocytes as shown by low levels of myeloperoxidase. Concomitantly, histol. examn. revealed significant protection against postischemic damages after AICAR **therapy**. High adenosine concns. induced by AICAR **treatment** **prevent** PMN leukocyte accumulation and activation within the intestinal ischemia during the postischemic phase, thus **preventing** the aggravation of mucosal lesions normally obsd. in untreated cats.

L85 ANSWER 56 OF 93 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
93283571 EMBASE Document No.: 1993283571. Xanthine oxidase activity in the circulation of rats following hemorrhagic shock. Tan S.; Yokoyama Y.; Dickens E.; Cash T.G.; Freeman B.A.; Parks D.A.. Department of Anesthesiology, University of Alabama, 619 South 19th Street,Birmingham, AL 35233-6810, United States. Free Radical Biology and Medicine 15/4 (407-414) 1993.
ISSN: 0891-5849. CODEN: FRBMEH. Pub. Country: United States. Language: English. Summary Language: English.

AB Reactive oxygen **metabolites** generated from xanthine oxidase play an important role in the pathogenesis of **ischemia**-induced **tissue** injury. In a hemorrhagic shock model of ischemia-reperfusion, the intracellular enzyme xanthine oxidase was

released into the vasculature. This intravascular source of superoxide (O2.-) and hydrogen peroxide (H2O2) interacted reversibly with glycosaminoglycans of vascular endothelium and markedly concentrated xanthine oxidase at cell surfaces, enhancing its ability to produce extensive damage to remote tissues. Rats were made hypotensive by hemorrhage, maintained for 2 h, and reinfused with shed blood. Blood samples were obtained prior to hemorrhage and 15, 30, 60, and 90 min after reperfusion for determination of xanthine oxidase (XO), lactate dehydrogenase (LDH), and alanine transaminase (AST). These enzymes were not significantly elevated in control animals. Reperfusion after hemorrhage-induced ischemia resulted in significantly elevated AST and LDH in both low heparin (100 U/h) and high heparin (1000 U/h) groups. Xanthine oxidase was detected in the circulation only after 90 min reperfusion in the low heparin group and was elevated during the entire reperfusion period in the high heparin group. Studies with cultured vascular endothelium showed significant heparin-reversible binding of XO to cellular glycosaminoglycans. These results suggest that XO can gain access to the circulation following ischemia, where it then binds to the vascular endothelial cells to produce site-specific oxidant injury to organs remote from the site of XO release.

L85 ANSWER 57 OF 93 CAPLUS COPYRIGHT 2003 ACS

1993:662470 Document No. 119:262470 Calcium antagonist and antiperoxidant properties of some hindered phenols. Sgaragli, G. P.; Valoti, M.; Gorelli, B.; Fusi, F.; Palmi, M.; Mantovani, P. (Ist. Sci. Farmacol., Siena, 53100, Italy). British Journal of Pharmacology, 110(1), 369-77 (English) 1993. CODEN: BJPCBM. ISSN: 0007-1188.

AB The calcium antagonist and antioxidant activities of certain synthetic and natural phenols, related to BHA (2-tert-butyl-4-methoxyphenol), were evaluated in rat ileal longitudinal muscle and in lipid peroxidn. models resp. Compds. with a phenol or a phenol deriv. moiety, with the exception of 2,2'-dihydroxy-3,3'-di-tert-butyl-5,5'-dimethoxydiphenol (di-BHA), inhibited in a concn.-dependent manner the BaCl2-induced contraction of muscle incubated in a Ca2+-free medium. Calcd. pIC50 (M) values ranged between 3.2 (probucol) and 4.96 [3,5-di-tert-butyl-4-hydroxyanisole (di-tert-BHA)], with intermediate activity shown by khellin < gossypol < **quercetin** < 3-tert-butylanisole < BHA < nordihydroguaiaretic acid (NDGA) < 2,6-di-tert-butyl-4-methylphenol (BHT) and papaverine. The Ca2+ channel activator Bay K 8644 overcame the inhibition sustained by nifedipine, BHA and BHT, while only partially reversing that of papaverine. BHA, BHT, nifedipine and papaverine also inhibited in a concn.-dependent fashion CaCl2 contractions of muscle depolarized by a K+-rich medium. This inhibition appeared to be inversely affected by the Ca2+-concn. used. The inhibitory effects of nifedipine, papaverine, BHA and BHT were no longer present when muscle contraction was elicited in skinned fibers by 5 .mu.M Ca2+ or 500 .mu.M Ba2+, suggesting a plasmalemmal involvement of target sites in spasmolysis. Comparative antioxidant capability was assessed in 2 peroxyl radical scavenging assay systems. These were based either on the oxidn. of linoleic acid initiated by a heat labile azo compd. or on lipid peroxidn. of rat liver microsomes promoted by Fe2+ ions. Across both model systems, di-tert-BHA, NDGA, BHT, di-BHA, BHA and **quercetin** ranked as the most potent inhibitors of lipid oxidn., with calcd. pIC50 (M) values ranging between 7.4 and 5.7,. Of the 32 compds. studied only 15 phenolic derivs. exhibited both antispasmogenic and antioxidant activity. Within this subgroup a linear and significant correlation was found between antispasmogenic activity and antioxidn. These bifunctional compds. were characterized by the presence of at least 1 hydroxyl group on the arom. ring and a highly lipophilic area in the mol. Di-tert-BHA is proposed as a lead ref. compd. for future synthesis of new antioxidants combining two potentially useful properties

Searched by: Mary Hale 308-4258 CM-1 1E01

in the **prevention** of **tissue** damage after **ischemia**-reperfusion injury.

L85 ANSWER 58 OF 93 MEDLINE

93178114 Document Number: 93178114. PubMed ID: 8440127. Long-chain acyl-coenzyme A thioesters and renal hypothermic ischemic injury: effects of glycine flush. Mangino M J; Murphy M K; Anderson C B. (Department of Surgery, Washington University School of Medicine, St. Louis, Missouri 63110.) CRYOBIOLOGY, (1993 Feb) 30 (1) 25-31. Journal code: 0006252. ISSN: 0011-2240. Pub. country: United States. Language: English.

AB The effects of hypothermic ischemia utilizing Euro-Collins flush on renal tissue long-chain activated fatty acid content was studied in dogs. Also, the ability of the simple amino acid glycine to complex these acyl thioesters was also investigated. Renal inner cortex was found to contain (in increasing amounts) myristoyl-, palmitoleoyl-, palmitoyl-, arachidonyl-, and oleoyl-coenzyme A throughout the 3 days of cold ischemia. Although the amounts of individual long-chain acyl-CoA compounds varied considerably, the concentrations were not found to differ significantly with increasing ischemia times. The presence of 5 mM of glycine in the flush also did not influence the amount or species of long-chain acyl-CoA esters in renal **tissue** during cold **ischemia**. Ischemic renal tissue content of most long-chain acyl-CoA compounds was reduced by about 50% when the tissue underwent in vitro reperfusion with 37 degrees C O2-saturated media. Glycine included in the flush storage solution did not alter acyl-CoA levels in **tissue** undergoing hypothermic **ischemia** and short-term in vitro reperfusion with O2-saturated buffer. In conclusion, long-chain acyl-CoA thioesters are present during hypothermic renal ischemia and the levels of most of these species are reduced during in vitro reperfusion after ischemia. The quality and production mass of these **metabolites** appears to be unaltered by progressive hypothermic ischemia times. Finally, the protective effects of glycine in this model of renal organ preservation injury are not associated with reductions of renal tissue long-chain activated fatty acids.

L85 ANSWER 59 OF 93 CAPLUS COPYRIGHT 2003 ACS

1992:188073 Document No. 116:188073 Antioxidants for the **prevention** and **treatment** of cardiac reperfusion injuries. Mickle, Donald A. G.; Wu, Tai Wing (Sterling Drug, Inc., USA). U.S. US 5080886 A 19920114, 7 pp. (English). CODEN: USXXAM. APPLICATION: US 1990-461599 19900105.

AB Administration of a pharmaceutical soln. contg. 6-hydroxy-2,5,7,8-tetramethylchroma-2-carboxylic acid (Trolox) (I), superoxide dismutase (II), catalase and/or ascorbic acid prior to or simultaneously with resuming normal blood supply to mammalian **tissue** following **ischemia** provides substantial protection from tissue damage resulting from the reperfusion. Cultured venticular myocytes were **treated** with xanthine oxidase and hypoxanthine followed by addn. of I 1 mM, II 107, and catalase 107IU/L. The time to necrose 105 cells was 8.07 as compared with 1.68 min for the control, indicating the combination was effective in protecting myocytes from free radical injury.

L85 ANSWER 60 OF 93 JICST-EPlus COPYRIGHT 2003 JST

920753747 **Vitamin E** in digestive diseases.. YOSHIKAWA TOSHIKAZU; NAITO YUJI; KONDO MOTOHARU. Kyoto Prefect. Univ. of Medicine. Kassei Sanso, Furi Rajikaru (Journal of Active Oxygens & Free Radicals). (1992) vol. 3, no. 5, pp. 597-602. Journal Code: L1066A (Fig. 5, Ref. 10) CODEN: KSFREC; CODEN: 0915-8847; Pub. Country: Japan. Language: Japanese.

AB Oxygen-derived free radicals have been reported to be closely involved in the development of several digestive diseases. Lipid peroxidation induced

Searched by: Mary Hale 308-4258 CM-1 1E01

by oxygen radicals is believed to be one of the improtant causes of biological membrane destruction and cell damage. **Vitamin E** levels in serum and digestive organ **tissues** significantly decreased after **ischemia**-reperfusion. In vitamine E-deficient animals, CCl4-induced liver injury and ischemia-reperfusion injury of the stomach were enhanced compared with **vitamin E**-sufficient rats. These results indicate that **vitamin E** is consumed in the process of lipid peroxidation induced by free radicals in some digestive diseases to **prevent** the development of tissue damage. (author abst.)

L85 ANSWER 61 OF 93 MEDLINE

92334310 Document Number: 92334310. PubMed ID: 1630435. Experimental studies on the effects of alpha-tocopherol in small intestinal ischemia and reperfusion injury. Hanai G; Kimura T; Shiraishi T; Sano M; Matsumoto S; Funabiki T; Yoshizaki S. (Department of Surgery, Fujita Gakuen Health University School of Medicine, Toyoake, Japan.) NIPPON GEKA GAKKAI ZASSHI. JOURNAL OF JAPAN SURGICAL SOCIETY, (1992 Jun) 93 (6) 589-98. Journal code: 0405405. ISSN: 0301-4894. Pub. country: Japan. Language: Japanese.

AB In the present study, we quantified the biochemical [thiobarbituric acid (TBA) reactants, superoxide dismutase (SOD) and **vitamin E**] and histologic changes in the small intestinal **tissue** after **ischemia** and/or reperfusion. Sixty-seven Wistar rats were divided into 7 groups; N group: control, A-I group: 30 min. ischemia, A-II group: 120 min. ischemia, B-I group: Declamp after 30 min. ischemia, B-II group: 30 min. reperfusion after 30 min. ischemia, B-III group: 30 min. reperfusion after 120 min. ischemia, E group: **vitamin E** administration 30 min. reperfusion after 30 min. ischemia. The levels of TBA reactants were significantly different between A-II and B-II, B-II and E (all p less than 0.01). For SOD, there were significant differences between N and B-I (p less than 0.01), N and E (p less than 0.05). For **vitamin E**, there were significant differences between A-I and B-I, A-I and B-I, B-II and E (all p less than 0.01). Histologic changes showed that the grade of tissue injury was more severe in B-I and B-II than in A-I, and was less in E than in B-II. It is suggested that **vitamin E** protected cells from injury due to oxygen free radicals.

L85 ANSWER 62 OF 93 MEDLINE DUPLICATE 15

93166941 Document Number: 93166941. PubMed ID: 1337651. Influence of anti-inflammatory drugs and free radical scavengers on intestinal **ischemia** induced oxidative **tissue** damage. Augustin A J; Goldstein R K; Milz J; Lutz J. (Physiologisches Institut der Universitaet, Wuerzburg, F.R.G.) ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1992) 316 239-51. Journal code: 0121103. ISSN: 0065-2598. Pub. country: United States. Language: English.

AB The influence of oxygen free radical scavengers and anti-inflammatory drugs on postischemic lipid peroxidation and myeloperoxidase activity was shown. The best results were obtained from **vitamin E** and the antiinflammatory **treatment** with CP and SUL, whereas an iron elimination only showed slight effects on myeloperoxidase activity above all. In experiments without **therapy** a linear increase of lipid peroxides dependent on reperfusion durance was found, whereas myeloperoxidase already showed a remarkable increase during ischemia and early reperfusion. This difference can be interpreted by scavenging mechanisms, which are overcharged after an appointed durance of reperfusion.

L85 ANSWER 63 OF 93 MEDLINE DUPLICATE 16

Searched by: Mary Hale 308-4258 CM-1 1E01

92193354 Document Number: 92193354. PubMed ID: 1548294. Hyperglycemic versus normoglycemic stroke: topography of brain **metabolites**, intracellular pH, and infarct size. Wagner K R; Kleinholz M; de Courten-Myers G M; Myers R E. (Research Service, Department of Veterans Affairs, Medical Center, Cincinnati, Ohio 45220.) JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, (1992 Mar) 12 (2) 213-22. Journal code: 8112566. ISSN: 0271-678X. Pub. country: United States. Language: English.

AB Hyperglycemia aggravates brain pathologic outcome following middle cerebral artery (MCA) occlusion in cats. We presently determined if hyperglycemia during occlusion leads to high lactic acid accumulations in the ischemic MCA territory. We measured brain metabolite concentrations in 14 MCA territory sites at 0.5 and 4 h following occlusion in hyper- (20 mM) and normoglycemic (5 mM) cats and correlated these results with previous brain pathologic findings. Hyper- versus normoglycemia during MCA occlusion resulted in significantly higher lactate concentrations in the ischemic territory and more numerous loci with lactates greater than 17 mumol/g. At 0.5 h of occlusion, ATP levels were lower in normoglycemic cats, while at 4 h, ATP was similarly reduced (40%) in both glycemia groups. At 4 h, PCr was more reduced in hyperglycemics secondary to a greater brain tissue acidosis. Carbohydrate substrates at 0.5 h were more markedly depleted in normoglycemics, likely limiting lactate accumulation (34.3% versus only 5.0% of sites in hyperglycemics with glucose less than 0.5 mumol/g). Although lactate was markedly elevated at both 0.5 and 4 h in hyperglycemic ischemic territories, clip release at 4 versus 0.5 h yields a significantly poorer brain pathologic outcome. Correspondingly, intracellular pH, calculated from the creatine kinase equilibrium, was more markedly depressed at 4 than at 0.5 h of occlusion, demonstrating a time-dependent dissociation between tissue lactate and hydrogen ion accumulations. The present findings show that following MCA occlusion (a) hyperglycemia increases the magnitude and topographic extent of marked tissue lactic acidosis, (b) infarct size following 0.5 h of clip release correlates more closely with tissue acidosis than with lactate concentrations, (c) ischemic tissue ATP concentrations correlate poorly with infarct size, (d) normoglycemia limits lactate accumulation during focal **ischemia** because **tissue** glucose is depleted, and (e) early during **ischemia**, **tissue** buffering or antiport mechanisms may **prevent** marked increases in intracellular hydrogen ion activity.

L85 ANSWER 64 OF 93 MEDLINE DUPLICATE 17

93117546 Document Number: 93117546. PubMed ID: 1475527. Changes in the xanthine dehydrogenase/xanthine oxidase ratio in the rat kidney subjected to ischemia-reperfusion stress: **preventive** effect of some **flavonoids**. Sanhueza J; Valdes J; Campos R; Garrido A; Valenzuela A. (Unidad de Bioquimica Farmacologica y Lipidos, INTA, Universidad de Chile, Santiago.) RESEARCH COMMUNICATIONS IN CHEMICAL PATHOLOGY AND PHARMACOLOGY, (1992 Nov) 78 (2) 211-8. Journal code: 0244734. ISSN: 0034-5164. Pub. country: United States. Language: English.

AB The enzyme xanthine oxidase has been implicated in the **tissue** oxidative injury after **ischemia**-reperfusion. This enzyme, which is a source of oxygen free radicals, is formed from a dehydrogenase form during ischemia. The ratio dehydrogenase/oxidase of rat kidney homogenates decreases during the ischemia and the reperfusion. Two **flavonoids**, **quercetin** and silybin, characterized as free radical scavengers, exert a protective effect **preventing** the decrease in the dehydrogenase/oxidase ratio observed during ischemia-reperfusion. The mechanism of this effect and the role of **flavonoids** in the **ischemia**-reperfusion **tissue** damage is discussed.

Searched by: Mary Hale 308-4258 CM-1 1E01

L85 ANSWER 65 OF 93 MEDLINE
92269309 Document Number: 92269309. PubMed ID: 1588606. Evidence for free radical mechanisms of brain injury resulting from ischemia/reperfusion-induced events. Kirsch J R; Helfaer M A; Lange D G; Traystman R J. (Department of Anesthesiology/Critical Care Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland.) JOURNAL OF NEUROTRAUMA, (1992 Mar) 9 Suppl 1 S157-63. Ref: 89. Journal code: 8811626. ISSN: 0897-7151. Pub. country: United States. Language: English.
AB Free radicals have been implicated in the injury that occurs to brain **tissue** in response to **ischemia** and reperfusion insults. Confirmatory in vivo studies have been limited by the difficulty in measuring free radicals in brain tissue. This review discusses potential mechanisms for free radical production in brain tissue and the evidence supporting the **therapeutic** efficacy of free radical scavengers. Free radicals may be produced during ischemia/reperfusion as a result of multiple mechanisms involving normal regulatory systems of intra-/extracellular metabolism. For example, metabolism of free fatty acids by the cyclo-oxygenase pathway and adenine nucleotides by xanthine oxidase has been proposed to produce free radical adducts during reperfusion. **Therapeutic** strategies aimed at decreasing brain injury from free radical production include administration of free radical scavengers at the time of reperfusion. Pharmacologic interventions for protection from free radical injury in brain are hindered because of limited access to the site of free production.

L85 ANSWER 66 OF 93 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 18
1992:208266 Document No.: BA93:108491. ISCHEMIA-REPERFUSION INJURY AND **VITAMIN E**. YOSHIKAWA T; TAKAHASHI S; KONDO M. FIRST DEP. MED., KYOTO PREFECTURAL UNIV. MED., KYOTO 606, JAPAN.. VITAMINS (KYOTO), (1992) 66 (2), 79-89. CODEN: BTMNA7. ISSN: 0006-386X. Language: Japanese.
AB Oxygen-derived free radicals have been reported to be closely involved in the development of **tissue** injury induced by **ischemia** -reperfusion in several organs, such as heart, brain, lung, liver, stomach, small intestine, kidney and so on. **Ischemia** itself causes **tissue** damage, but further injuries can occur when oxygen is reintroduced to the tissue. Furthermore, lipid peroxidation mediated by free radicals is believed to be one of the important causes of biological membrane destruction and cell damage. It has been reported that **Vitamin E** exists in the cell membrane of various tissues and functions as a lipid-soluble antioxidant by scavenging oxygen-derived free radicals and terminating free radical chain reaction. In experimental ischemia-reperfusion injury model, **Vitamin E** in the tissue was significantly decreased after ischemia-reperfusion. On the other hand, in **Vitamin E**-deficient animals, ischemia-reperfusion injury was more severe than in **Vitamin E**-nondeficient animals. These results indicate that **Vitamin E** is consumed in the process of lipid peroxidation induced by free radicals in ischemia-reperfusion to **prevent** the development of tissue damage.

L85 ANSWER 67 OF 93 MEDLINE DUPLICATE 19
91124369 Document Number: 91124369. PubMed ID: 1992125. A cardioselective, hydrophilic N,N,N-trimethylethanaminium alpha-tocopherol analogue that reduces myocardial infarct size. Grisar J M; Petty M A; Bolkenius F N; Dow J; Wagner J; Wagner E R; Haegele K D; De Jong W. (Merrell Dow Research Institute, Strasbourg, France.) JOURNAL OF MEDICINAL CHEMISTRY, (1991 Jan) 34 (1) 257-60. Journal code: 9716531. ISSN: 0022-2623. Pub. country: United States. Language: English.
AB The alpha-tocopherol analogue 3,4-dihydro-6-hydroxy-N,N,N,2,5,7,8-

Searched by: Mary Hale 308-4258 CM-1 1E01

heptamethyl-2H-1-**benzopyran**-2-ethanaminium 4-methylbenzenesulfonate (1a, MDL 73404) and its O-acetate 1b (MDL 74270) were synthesized. Compound 1a was found to be hydrophilic (log P = -0.60) and to **prevent** lipid autoxidation in rat brain homogenate with an IC50 of 1.7 +/- 0.9 microM. Tissue distribution studies with [14C]-1b in rats (1 mg/kg iv) showed that radioactivity accumulates in the heart (ratio 20:1 vs blood after 1 h). Infusion of 1 mg/kg per h of 1b bromide reduced infarct size by 54% in rats subjected to coronary artery occlusion for 60 min followed by reperfusion for 30 min, compared to saline-infused controls. By comparison, the tertiary amine analogue 5 was found not to accumulate in heart tissue, to be an equally effective free-radical scavenger in vitro, but to require a higher dose to reduce infarct size in rats. This shows that the cardioselectivity of compound 1 contributes to its potency in salvaging myocardial **tissue** in rats after **ischemia** and reperfusion.

L85 ANSWER 68 OF 93 MEDLINE

92015002 Document Number: 92015002. PubMed ID: 1920254. Endotoxemia in horses. A review of cellular and humoral mediators involved in its pathogenesis. Morris D D. (Department of Large Animal Medicine, College of Veterinary Medicine, University of Georgia, Athens 30602.) JOURNAL OF VETERINARY INTERNAL MEDICINE, (1991 May-Jun) 5 (3) 167-81. Ref: 285. Journal code: 8708660. ISSN: 0891-6640. Pub. country: United States. Language: English.

AB Endotoxemia remains the leading cause of death in horses, being intimately involved in the pathogenesis of gastrointestinal disorders that cause colic and neonatal foal septicemia. Endotoxins, normally present within the bowel, gain access to the blood across damaged intestinal mucosa, or endotoxemia occurs when gram negative organisms proliferate in tissues. Endotoxins are removed from the circulation by the mononuclear phagocyte system, and the response of mononuclear phagocytes to these lipopolysaccharides (LPS) play an important role in determining the severity of clinical disease. Macrophages become highly activated for enhanced secretory, phagocytic and cidal functions by LPS. Macrophage-derived cytokines are responsible for many of the pathophysiologic consequences of endotoxemia. The arachidonic acid **metabolites**, prostacyclin and thromboxane A2 likely mediate early hemodynamic dysfunction and the leukotrienes may potentiate **tissue ischemia** during endotoxemia. Interleukin 1 (IL-1) induces fever and is responsible for the inflammatory cascade, which constitutes the acute phase response. Tumor necrosis factor (TNF), an important proximal mediator of the effects of LPS, acts to initiate events and formation of other molecules that affect shock and tissue injury. Systemic administration of TNF produces most of the physiologic derangements that are associated with endotoxemia and antibodies that are directed against TNF significantly reduce LPS-induced mortality in experimental animals. In response to endotoxins, mononuclear phagocytes express thromboplastin-like procoagulant activity (PCA), which initiates microvascular thrombosis. Both IL-1 and TNF induce PCA expression, creating a positive feedback loop for LPS-induced coagulopathy. A macrophage-derived platelet activating factor contributes to coagulation dysfunction and further stimulates arachidonic acid metabolism. The ultimate consequences of endotoxemia are multiple system organ failure and death. The numerous feedback loops and intertwining cascades of mediators during endotoxemia defy simplistic methods of **treatment**. The optimal **therapy** likely involves methods to alter the generation of inflammatory mediators by mononuclear phagocytes.

L85 ANSWER 69 OF 93 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 20

1991:505748 Document No. 115:105748 Protective effects of **quercetin**

Searched by: Mary Hale 308-4258 CM-1 1E01

on ischemic reperfusion-induced arrhythmias in the rat heart in vivo. Xie, Meilin; Gu, Zhenlun; Qian, Zengnian (Dep. Pharmacol., Suzhou Med. Coll., Suzhou, 215007, Peop. Rep. China). Zhongguo Yaolixue Yu Dulixue Zazhi, 5(2), 90-2 (Chinese) 1991. CODEN: ZYYZEW. ISSN: 1000-3002.

AB Reperfusion-induced arrhythmias were elicited in the pentobarbitone-anesthetized rat by the ligation of the left main coronary artery and subsequent release. To observe the protective effects of **quercetin** on reperfusion-induced arrhythmias, the authors measured the malondialdehyde (MDA), superoxide dismutase (SOD), and xanthine oxidase (XOD) of myocardial tissues, together with a record of std. lead II ECG. When **quercetin** (0.5 mmol/L, 10 mL/kg) was administered i.v. 1 min before the ligature released and 2 min after reperfusion, it reduced the incidence of ventricular fibrillation, shortened the duration of reperfusion-induced arrhythmias, effectively protected the activity of SOD, and decreased the activity of XOD and the content of MDA in **ischemia**-reperfusion myocardial **tissues**. The results suggested that the mechanism of the antiarrhythmic effect of **quercetin** was assocd. with the inhibition of the generation of oxygen free radicals, with the **prevention** of inactivation of SOD and/or with the direct scavenging of oxygen free radicals in the myocardial tissues.

L85 ANSWER 70 OF 93 MEDLINE DUPLICATE 21

91313880 Document Number: 91313880. PubMed ID: 1858332. [The effect of gamma-hydroxybutyric acid on the reaction rate of phosphate-containing **metabolites** in the rat brain during ischemia estimated from (31)P-NMR spectroscopic data]. Vliianie GOMK na tempy snizheniia makroergicheskikh fosfatov mozga krys vo vremia ishemii po dannym prizhiznennoi (31)P-YaMR-spektroskopii. Likhova S S; Likhodii S S; Sibel'dina L A. VOPROSY MEDITSINSKOI KHIMII, (1991 Jan-Feb) 37 (1) 19-21. Journal code: 0416601. ISSN: 0042-8809. Pub. country: USSR. Language: Russian.

AB Protective effects of gamma-hydroxybutyric acid on bioenergetic reactions were studied in brain of rats with ischemia using 31P-NMR spectroscopy in vivo. Intraperitoneal preadministration of gamma-hydroxybutyric acid at a dose of 400 mg/kg within 30-40 min before ischemia led to a decrease in the ATP pool in ischemic brain tissue, to alteration in the PCr/ATP ratio in the 31P-NMR spectrum, to **prevention** of Pi concentration increase and to increase in the intracellular acidosis development rate. Possible mechanisms of the gamma-hydroxybutyric acid effects on bioenergetic reactions in nervous **tissue** during **ischemia** are discussed.

L85 ANSWER 71 OF 93 MEDLINE DUPLICATE 22

91039341 Document Number: 91039341. PubMed ID: 2231733. Improved post-ischemic ventricular recovery in the absence of changes in energy metabolism in working rat hearts following heat-shock. Currie R W; Karmazyn M. (Department of Anatomy, Dalhousie University, Halifax, Nova Scotia, Canada.) JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, (1990 Jun) 22 (6) 631-6. Journal code: 0262322. ISSN: 0022-2828. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We have previously demonstrated that induction of the heat-shock response in rats results in improved recovery of isolated Langendorff-perfused rat hearts subjected to low-flow ischemia followed by reperfusion (Currie et al., 1988). The mechanisms underlying this protective effect of heat-shock are uncertain although the protection was associated with enhanced content of the antioxidant enzyme catalase but not superoxide dismutase or glutathione peroxidase (Currie et al., 1988). Various investigators have suggested the importance of improved energy metabolism in determining recovery following ischemia (Pasque and Wechsler, 1984;

Haas et al., 1984; Devous and Lewandowski, 1987). We therefore examined, using a working rat heart model subjected to 10 or 15 min zero flow ischemia whether changes in energy **metabolites** could account for the protective effect of the heat-shock response. Hearts perfused 24 h after induction of heat-shock failed to demonstrate significant improvement of recovery following 10 min ischemia, however recovery was significantly enhanced in hearts reperfused after 15 min ischemia. Ischemia produced a depression in both ATP and creatine phosphate (CP) content whereas a moderate elevation in ADP and AMP and a marked increase in tissue lactate were evident. These changes were unaffected by prior heat-shock **treatment**. For both durations of **ischemia** **tissue metabolites** were determined during early (5 min) and late (30 min) reperfusion. Although partial recovery in high energy phosphates and a return of ADP, AMP and lactate to near-normal levels were evident, no differences in energy products were observed between hearts from normal or heat-shocked animals, in spite of significantly enhanced recovery.(ABSTRACT TRUNCATED AT 250 WORDS)

L85 ANSWER 72 OF 93 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 23

1990:474970 Document No.: BA90:114390. EFFECTS OF BUNAZOSIN A SELECTIVE ALPHA-1-ADRENERGIC BLOCKING AGENT ON MYOCARDIAL ENERGY METABOLISM IN ISCHEMIC DOG HEART. YOSHIDA R; ICHIHARA K; ABIKO Y. DEP. PHARMACOL., ASAHIKAWA MED. COLL., 4-5 NISHIKAGURA, ASAHIKAWA 078, JPN.. JPN J PHARMACOL, (1990) 53 (4), 435-442. CODEN: JJPAAZ. ISSN: 0021-5198. Language: English.

AB Effects of a selective .alpha.1-adrenergic blocking agent, bunazosin, on myocardial energy metabolism in the ischemic heart were studied. Ischemia was induced by ligating the left anterior descending coronary of the dog heart. Bunazosin was injected intravenously either 5 or 20 min before coronary artery ligation. Hearts were removed 3 min after coronary ligation and used for determination of the levels of cardiac **tissue metabolites**. **Ischemia** decreased the levels of ATP, creatine phosphate, glycogen and glucose, and increased the levels of ADP, AMP, hexose monophosphates and lactate. The energy charge potential (ECP) calculated was decreased by ischemia. Pretreatment with bunazosin inhibited the decrease in ATP and the increase in AMP caused by ischemia, resulting in the high value of ECP in the ischemic myocardium. Bunazosin also **prevented** the changes in carbohydrate metabolism caused by ischemia. It is concluded that bunazosin may reduce the influence of ischemia on the myocardium.

L85 ANSWER 73 OF 93 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 24

1990:446279 Document No.: BA90:96919. MECHANISMS OF GASTROPROTECTION. KONTUREK S J. INST. PHYSIOL., ACAD. MED., 31-531 KRAKOW, UL. GRZEGORZECKA 16, POLAND.. SCAND J GASTROENTEROL SUPPL, (1990) 25 (174), 15-28. CODEN: SJGSB8. ISSN: 0085-5928. Language: English.

AB Gastric mucosa is constantly exposed to various irritants, but it usually maintains its integrity owing to several lines of defense, including mucus-alkaline secretion, mucosal hydrophobicity, rich mucosal blood flow, stabilization of tissue lysosomes, maintenance of mucosal sulfhydryls, and rapid proliferation and renewal of mucosal cells. Prostaglandins (PG) inhibit experimental gastric mucosal damage and ulcerations induced by a wide variety of agents, hence PG have been proposed to contribute to the overall protective process by activation of various mucosal defence lines-particularly by **prevention** of vasocongestion, ischemia, and deep hemorrhagic necrosis. The relation between tissue PG generation and mucosal protection does not appear to be closely related, and probably only minute amounts of PG are required to maintain mucosal integrity. In

contrast to PG, other products of arachidonate metabolism, such as TxA2, LTC4 or LTD4, and the related lipid, platelet-activating factor, appear to mediate mucosal damage mainly by the disturbance in mucosal microcirculation and **tissue ischemia**. Gastroprotection can be achieved by stimulation of mucosal biosynthesis of protective PG or by the inhibition of the release or action of the proulcerogenic arachidonate **metabolites**. Certain natural substances, such as sulfhydryls, epidermal growth factor, or polyamines, protect the mucosa via a PG-independent mechanism, probably by enhancing the tissue repair processes. The resistance of mucosa to injury can be also increased by challenging with mild irritants ('adaptive cytoprotection'), and this attributed to the stimulation of mucosal PG biosynthesis, but a certain role may also be played by a physical barrier formed from the alkaline mucoid debris ('mucoid cap'), which mitigates the effects of subsequent exposure to the necrotizing agents and permits rapid epithelial repair and reconstitution. Some anti-ulcer drugs, which are believed to act primarily by neutralization of gastric acid (antacids) or by coating the mucosa (sucralfate, colloidal bismuth preparations), have been reported to have gastroprotective properties against various irritants, possibly due to the stimulation of mucosal production of PG. Protection of human gastroduodenal mucosa by PG and other gastroprotective agents against the challenge by irritants such as aspirin or ethanol has been demonstrated, and the clinical benefit of these agents in the **therapy** of peptic ulceration is currently under active investigation.

L85 ANSWER 74 OF 93 MEDLINE

90385197 Document Number: 90385197. PubMed ID: 2205898. Mechanisms of gastroprotection. Konturek S J. (Institute of Physiology, Academy of Medicine, Cracow, Poland.) SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY. SUPPLEMENT, (1990) 174 15-28. Ref: 79. Journal code: 0437034. ISSN: 0085-5928. Pub. country: Norway. Language: English.

AB Gastric mucosa is constantly exposed to various irritants, but it usually maintains its integrity owing to several lines of defense, including mucus-alkaline secretion, mucosal hydrophobicity, rich mucosal blood flow, stabilization of tissue lysosomes, maintenance of mucosal sulfhydryls, and rapid proliferation and renewal of mucosal cells. Prostaglandins (PG) inhibit experimental gastric mucosal damage and ulcerations induced by a wide variety of agents, hence PG have been proposed to contribute to the overall protective process by activation of various mucosal defence lines--particularly by **prevention** of vasocongestion, ischemia, and deep hemorrhagic necrosis. The relation between tissue PG generation and mucosal protection does not appear to be closely related, and probably only minute amounts of PG are required to maintain mucosal integrity. In contrast to PG, other products of arachidonate metabolism, such as TxA2, LTC4 or LTD4, and the related lipid, platelet-activating factor, appear to mediate mucosal damage mainly by the disturbance in mucosal microcirculation and **tissue ischemia**. Gastroprotection can be achieved by stimulation of mucosal biosynthesis of protective PG or by the inhibition of the release or action of the proulcerogenic arachidonate **metabolites**. Certain natural substances, such as sulfhydryls, epidermal growth factor, or polyamines, protect the mucosa via a PG-independent mechanism, probably by enhancing the tissue repair processes.(ABSTRACT TRUNCATED AT 250 WORDS)

L85 ANSWER 75 OF 93 MEDLINE

90302447 Document Number: 90302447. PubMed ID: 2363249. [The effect of alpha-tocopherol and lidocaine on the structural-functional rearrangement of liver endoplasmic reticulum membranes after induction with phenobarbital in the postischemic period]. Vliianie alpha-tokoferola i lidokaina na strukturno-funktsional'nuiu perestroiku membran

Searched by: Mary Hale 308-4258 CM-1 1E01

endoplazmaticheskogo retikuluma pecheni pri induktsii fenobarbitalom v postishemicheskom periode. Sharapov V I; Grek O R; Zykov A A. VOPROSY MEDITSINSKOI KHIMII, (1990 Mar-Apr) 36 (2) 14-8. Journal code: 0416601. ISSN: 0042-8809. Pub. country: USSR. Language: Russian.

AB Inhibition of an increase in total content of unsaturated fatty acids in microsomal lipids induced by phenobarbital, alterations of parameters of the fluorescent probe 1,8-ANS-binding with membranes as well as restrictions in induction of liver microsomal monooxygenase enzymatic system were detected during postischemic period after total liver **tissue ischemia**. Preadministration of alpha-tocopherol and lidocaine **prevented** distinctly the structure-functional alterations induced by phenobarbital in liver microsomal membranes during postischemic period. Possible factors responsible for limitations of the phenobarbital inducing effect during postischemic period are discussed.

L85 ANSWER 76 OF 93 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

1990:288661 Document No.: BA90:19507. LEUKOTRIENE-RECEPTOR ANTAGONIST FPL-55712 AND T-PA-INDUCED THROMBOLYSIS IN CANINE CORONARY THROMBOSIS. MEHTA J L; NICHOLS W W. UNIV. FLA., DEP. MED., BOX J-277, JHMHC, GAINESVILLE, FLA. 326.. THROMB RES, (1990) 58 (1), 13-22. CODEN: THBRAA. ISSN: 0049-3848. Language: English.

AB Leukocyte-derived arachidonate products peptido-leukotrienes have been shown to induce coronary constriction and platelet aggregation. As such, leukocytes may have a role in coronary thrombosis and coronary re-occlusion following thrombolysis. In the present study, we examined the effects of tissue-plasminogen activator (t-PA, 0.75 mg/kg over 20 minutes) given after either saline or FPL-55712 (2 mg/kg), a peptido-leukotriene receptor antagonist, in dogs with electrically-induced coronary thrombosis. Peripheral blood neutrophil number and superoxide anion generation increased ($P < 0.01$) during formation of thrombus and subsequent t-PA administration in saline-**treated** dogs. FPL-55712 pretreatment attenuated ($P < 0.05$) the increase in number of and superoxide anion generation by neutrophils. However, frequency of thrombolysis, duration of stored flow and re-occlusion rates were similar (P-NS) in both groups of dogs. This study shows that FPL-55712 does not modulate the thrombolytic potential of t-PA even though it decreases neutrophil activation in response to myocardial ischemia.

L85 ANSWER 77 OF 93 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 25

1989:337838 Document No.: BA88:40838. PYRUVATE DEHYDROGENASE ACTIVITY IN THE RAT CEREBRAL CORTEX FOLLOWING CEREBRAL ISCHEMIA. CARDELL M; KOIDE T; WIELOCH T. LAB. EXP. BRAIN RES., LUND HOSP., LUND, SWED.. J CEREB BLOOD FLOW METAB, (1989) 9 (3), 350-357. CODEN: JCBMDN. ISSN: 0271-678X. Language: English.

AB The effect of cerebral ischemia on the activity of pyruvate dehydrogenase (PDH) enzyme complex (PDHC) was investigated in homogenates fo froxen ratcerebral cortex followign 15 min of bilateral common carotid occulusion ischemia and following 15 min, 60 min, and 6 h of recirculation after 15 min of **ischemia**. In frozen cortical **tissue** from the same animals, the levels of labile phosphate compounds, glucose, glycogen, lactate, and pyruvate were determined. In cortex from control animals, the rate of [1-14C]pyruvate decarboxylation was 9.6 .+-. nmol CO2(min-mg protein) or 40% of the total PDHC activity. This fraction increased to 89% at the end of 15 min of ischemia. At 15 min of recirculation following 15 min of ischemia, the PDHC activity decreased to 50% of control levels and was drpressed for up to 6 h post ischemia. This decrease in activity was not due to a decrease in total PDHC activity. Apart from a reduction in ATP levels, the acute changes in the levels of energy **metabolites** were essentially normalized at 6 H of recovery. Dichloracetate (DCA), an

inhibitor of PDH kinase, given to rats at 250 mg/kg i.p. four times over 2 h, significantly decreased blood glucose levels form 7.4 .+-. 0.6 to 5.1 to 0.3 mmol/L and fully activated PDHC. In animals in which the plasma glucose level was maintained at control levels of 8.3 .+-. 0.5 .mu.mol/g by intravenous infusion of glucose, the active portion of PDHC increased to 95 .+-. 4%. In contrast, the depressed PDHC activity at 15 min followign ischemia was not affected by the DCA **treatment**. In both DCA + glucose-**treated** control and recovery groups, the pyruvate levels decreased by 50%. No significant difference in the lactate levels was seen. We conclude that the depressed postischemic PDHC activity is not due to loss of enzyme protein nor to an increased PDH kinase activity, but is probably due to a decrase activity of PDH phosphatase. This could in turn be secondary to a change in the cellular levels of PDG phosphatase regulators, most probably a decreased intramitochondrial concentration of calcim. The postischemic decreases in PDH activity may be related to the postichemic metabolic depression.

L85 ANSWER 78 OF 93 CAPLUS COPYRIGHT 2003 ACS
1989:229282 Document No. 110:229282 Oxygen radicals: mediators of gastrointestinal pathophysiology. Parks, Dale A. (Dep. Anesthesiol., Univ. Alabama, Birmingham, AL, 35294, USA). Gut, 30(3), 293-8 (English) 1989. CODEN: GUTTAK. ISSN: 0017-5749.

AB A review with 35 refs. Reactive O **metabolites** are probably responsible for the tissue injury obsd. in several tissues of the gastrointestinal tract after ischemia and reperfusion. The formation of O radicals from xanthine oxidase is considered a primary mechanism of **tissue** injury assocd. with **ischemia** reperfusion. There is addnl. evidence that neutrophils play a major role in ischemia-induced injury. Considerable progress has also been made in defining the role of O radicals in ischemic injury using indirect approaches such as administration of antioxidants. Existing data would suggest **therapeutic** efficacy of antioxidant enzymes.

L85 ANSWER 79 OF 93 MEDLINE
90060893 Document Number: 90060893. PubMed ID: 2583548. Role of oxygen-derived free radicals in gastric mucosal injury induced by ischemia or ischemia-reperfusion in rats. Yoshikawa T; Ueda S; Naito Y; Takahashi S; Oyamada H; Morita Y; Yoneta T; Kondo M. (First Department of Medicine, Kyoto Prefectural University of Medicine, Japan.) FREE RADICAL RESEARCH COMMUNICATIONS, (1989) 7 (3-6) 285-91. Journal code: 8709453. ISSN: 8755-0199. Pub. country: Switzerland. Language: English.

AB Oxygen-derived free radicals have been implicated as possible mediators in the development of **tissue** injury induced by **ischemia** and reperfusion. Clamping of the celiac artery in rats reduced the gastric mucosal blood flow to 10% of that measured before the clamping. The area of gastric erosions and thiobarbituric acid (TBA) reactants in gastric mucosa were significantly increased 60 and 90 min after clamping. These changes were inhibited by **treatment** with SOD and catalase. Thirty and 60 min after reoxygenation. produced by removal of the clamps following 30 min of ischemia, gastric mucosal injury and the increase in TBA reactants were markedly aggravated compared with those induced by ischemia alone. SOD and catalase significantly inhibited these changes. The serum alpha-tocopherol/cholesterol ratio, an index of in vivo lipid peroxidation, was significantly decreased after long periods of ischemia (60 and 90 min), or after 30 and 60 min of reperfusion following 30 min of ischemia. These results indicated that active oxygen species and lipid peroxidation may play a role in the pathogenesis of gastric mucosal injury induced by both ischemia alone and ischemia-reperfusion. Although, allopurinol inhibited the formation of gastric mucosal injury and the increase in TBA reactants in gastric mucosa, the depletion of

Searched by: Mary Hale 308-4258 CM-1 1E01

polymorphonuclear leukocytes (PMN) counts induced by an injection of anti-rat PMN antibody did not inhibit these changes. As compared with the hypoxanthine-xanthine oxidase system. PMN seem to play a relatively small part in the formation of gastric mucosal injury induced by ischemia-reperfusion.

L85 ANSWER 80 OF 93 MEDLINE DUPLICATE 26
90040750 Document Number: 90040750. PubMed ID: 2810381. Correlation between attenuation of posttraumatic spinal cord **ischemia** and preservation of **tissue vitamin E** by the 21-aminosteroid U74006F: evidence for an in vivo antioxidant mechanism. Hall E D; Yonkers P A; Horan K L; Braughler J M. (Central Nervous System Diseases Research Unit, Upjohn Company, Kalamazoo, Michigan.) JOURNAL OF NEUROTRAUMA, (1989 Fall) 6 (3) 169-76. Journal code: 8811626. ISSN: 0897-7151. Pub. country: United States. Language: English.
AB In the present study, the ability of U74006F, the 21-aminosteroid inhibitor of lipid peroxidation, to attenuate posttraumatic spinal cord ischemia has been examined in cats following a moderately severe compression injury. Moreover, in an attempt to assess whether U74006F is affecting in vivo posttraumatic lipid peroxidation, the effect of the compound on injury-induced spinal tissue **vitamin E** depletion was also studied. Following an initial 10 min postinjury hyperperfusion (+45%), spinal cord blood flow (SCBF) returned to the preinjury level at 30 min before entering a phase of progressive hypoperfusion, which reached -42.0 +/- 4.5% by 4 h postinjury in the vehicle-**treated** animals. In animals that received 30 min postinjury U74006F i.v. doses of 1.0, 3.0, or 10 mg/kg (plus 0.5, 1.5, and 5.0 mg/kg maintenance doses at 2.5 h.), the SCBF decline was reduced to -23.1%, -22.9%, and -26.1%, respectively (p less than 0.05 vs. vehicle at all three doses). A 0.3 mg/kg dose did not reduce the posttraumatic fall in SCBF. In vehicle-**treated** cats, the **vitamin E** content of the injured cord segment was reduced by 78.9% at 4 h postinjury in comparison to cord samples from uninjured vehicle-**treated** cats. In contrast, the same doses of U74006F (1.0, 3.0, and 10 mg/kg) that attenuated posttraumatic ischemia also significantly reduced the depletion of cord **vitamin E**. The lowest U74006F dosage (0.3 mg/kg), which failed to affect posttraumatic ischemia development, also had no effect on spinal cord **vitamin E** content.(ABSTRACT TRUNCATED AT 250 WORDS)

L85 ANSWER 81 OF 93 CAPLUS COPYRIGHT 2003 ACS
1989:560237 Document No. 111:160237 ATP **metabolites** as protectors of myocardial **tissues** in **ischemia**. Takeo, So (Japan). Jpn. Kokai Tokkyo Koho JP 63303927 A2 19881212 Showa, 8 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1987-140445 19870604.
AB Adenosine, inosine, and hypoxanthine are used for the **treatment** of myocardial ischemia. An injection soln. was prepd. contg. 2% adenosine in 10 mL according to the formulation method described in the Japanese Pharmacopeias (A-107).

L85 ANSWER 82 OF 93 MEDLINE
89059385 Document Number: 89059385. PubMed ID: 3195132. [Changes in the lipid component of liver microsomal membranes during the postischemic period after administration of alpha-tocopherol and lidocaine]. Izmeneniia lipidnogo komponenta mikrosomal'nykh membran pecheni v postishemicheskom periode pri vvedenii alpha-tokoferola i lidokaina. Grek O R. VOPROSY MEDITSINSKOI KHIMII, (1988 Jul-Aug) 34 (4) 57-63. Journal code: 0416601. ISSN: 0042-8809. Pub. country: USSR. Language: Russian.
AB Administration of alpha-tocopherol in combination with lidocaine **prevented** distinct alterations in lipid component of liver

Searched by: Mary Hale 308-4258 CM-1 1E01

microsomal membranes of rats during the restoration period after 30 min total **ischemia** of liver **tissue**. These drugs reduced the ratio of saturated and unsaturated fatty acids down to the initial level within 3 days after ischemia, whereas the alterations in fatty acid composition were maintained within 21 days of the restoration period in control experiment. Considerable alterations in the patterns of fluorescent probe ANS binding with microsomal membranes during the postischemic period were not observed after administration of the drugs. Protective effect of the drugs involved transformation of lipid component in microsomal membranes.

L85 ANSWER 83 OF 93 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

88247116 EMBASE Document No.: 1988247116. Ischemia at the crossroads?. Hearse D.J.. Rayne Institute, St Thomas' Hospital, London SE1 7EH, United Kingdom. Cardiovascular Drugs and Therapy 2/1 (9-15) 1988. ISSN: 0920-3206. CODEN: CDTHET. Pub. Country: United States. Language: English. Summary Language: English.

AB Understanding and controlling the consequences of myocardial ischemia requires us to acknowledge that we are dealing with a complex, dynamic, and highly variable process. The severity and progression of ischemic injury is not solely determined by the extent of oxygen deprivation, but by many other factors, including the accumulation of toxic **metabolites**. It may not be justified to assume that injury to the myocyte necessarily determines the survival of the organ; other components, such as the endothelium and the conducting system, may play a crucial role. Many factors can influence the severity and evolution of ischemic injury, perhaps the most important being the extent of residual (or collateral) flow to the affected **tissue**. If the **ischemia** is relatively mild, then the myocardium may survive for some long time, and drugs and other interventions may be used to further extend this period. However, reperfusion and the establishment of an adequate level of coronary flow is an absolute prerequisite for sustained tissue survival. The more severe the ischemia, the earlier must be the reperfusion. However, reperfusion of previously ischemic tissue is not without hazard, and it may precipitate potentially lethal events such as arrhythmias. Reperfusion may possibly result in the death of cells that were potentially viable in the moments before reflow was established, and there is good evidence that manipulation of reperfusion conditions may accelerate and possibly enhance recovery from ischemia. Much remains to be learned about myocardial ischemia and reperfusion, and in doing this we should perhaps put some of the older, yet well established, concepts behind us.

L85 ANSWER 84 OF 93 CAPLUS COPYRIGHT 2003 ACS

1987:400821 Document No. 107:821 Protective effects of free radical scavenger and antioxidant administration on ischemic liver cell injury. Marubayashi, S.; Dohi, K.; Ochi, K.; Kawasaki, T. (Sch. Med., Hiroshima Univ., 734, Japan). Transplantation Proceedings, 19(1, Book 2), 1327-8 (English) 1987. CODEN: TRPPA8. ISSN: 0041-1345.

AB The administration of **vitamin E** (VE) or glutathione (GSH) enhanced the level of VE and GSH in the liver, resp., and **prevented** the decreases in **tissue** antioxidants during liver **ischemia** and reperfusion. In CoQ10-**treated** animals, changes in VE and GSH were also completely **prevented**. Antioxidants pretreatment also completely suppressed the elevation of lipid peroxide during the reperfusion. GSH also accelerated the resynthesis of hepatic cellular ATP during the reperfusion. Thus, cell damage in hepatic ischemia and reperfusion is caused by free radical reaction processes, and the administration of free radical scavengers and antioxidants (VE, CoQ10, or GSH) is effective in the **treatment**

Searched by: Mary Hale 308-4258 CM-1 1E01

of ischemic liver injury.

L85 ANSWER 85 OF 93 MEDLINE
92173500 Document Number: 92173500. PubMed ID: 2979987. Mechanisms of myocardial cell injury during ischemia and reperfusion. Barry W H. (Department of Medicine, University of Utah School of Medicine, Salt Lake City 84132.) JOURNAL OF CARDIAC SURGERY, (1987 Sep) 2 (3) 375-83. Ref: 71. Journal code: 8908809. ISSN: 0886-0440. Pub. country: United States. Language: English.

AB **Ischemia** in myocardial **tissue** results in impaired high energy phosphate production and diminished perfusion of the interstitial space. Reduction in the supply of ATP to the sarcolemmal and sarcoplasmic reticulum Na+ and Ca2+ pumps results in a rise in intracellular (Ca2+), which can exceed normal systolic levels within 10 to 15 minutes. Elevated (Ca2+)i can cause activation of proteases and phospholipases, which can damage the sarcolemma and release toxic **metabolites**, such as lysophospholipids. Oxygen free radicals can be produced by breakdown of nucleosides and accumulate in the interstitial space. Accumulation of **metabolites** intracellularly can cause cell swelling, which in addition to rigor due to ATP depletion, can stress the weakened sarcolemma, producing cell rupture and death. With reperfusion, additional injury to the myocyte may occur. Resupply of oxygen can result in a burst of oxygen free radical production. Resynthesis of ATP may sensitize the myofilaments to Ca2+, resulting in a hypercontracture that can further promote cell rupture. Resupply of ATP and washout of H+ may cause activation of Na/Ca2+ exchange, thus intensifying Ca2+ overload. Washout of the hypertonic interstitial space fluid may aggravate cell swelling and produce sarcolemmal rupture. **Prevention** or alteration of ischemic and reperfusion injury in myocardial cells is important clinically. Strategies currently being explored include reducing the rise in (Ca2+)i, which occurs during ischemia and reperfusion; inhibiting the actions of phospholipase on the cell membrane; decreasing free radical effects; and reducing stress on the sarcolemmal by **prevention** of cell swelling and hypercontracture.

L85 ANSWER 86 OF 93 CAPLUS COPYRIGHT 2003 ACS
1987:155142 Document No. 106:155142 Role of toxic oxygen **metabolites** in **tissue ischemia**: an overview of recent progress in laboratory models of human disease. Bulkley, G. B.; Morris, J. B. (Dep. Surg., Johns Hopkins Med. Inst., Baltimore, MD, USA). Proc. Int. Congr. Nutr., 13th, Meeting Date 1985, 593-7. Editor(s): Taylor, T. Geoffrey; Jenkins, N. K. Libbey: London, UK. (English) 1986. CODEN: 55MOAW.

AB A review with 46 refs. on the mechanism of ischemic damage to heart, kidney and other tissues and ways for **therapeutic** intervention. Free-radical mediated tissue injury and its control in studies with human disease models are discussed. The role of free radical generation during reperfusion and mechanisms of ischemic injuries to gastrointestinal tract, skin, and heart are detailed.

L85 ANSWER 87 OF 93 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
1987:377326 Document No.: BA84:63823. ISCHEMIA AND REPERFUSION-INDUCED ARRHYTHMIAS IN THE ANESTHETIZED RAT EFFECT OF UBIQUINONE ALPHA TOCOPHEROL AND SUPEROXIDE DISMUTASE. SARRET M; AGOZZINO S; BELLAVITE O; PERUZZI M; CREMONESI P. CENTRO RICERCHE ITALFARMACO, VIA DEI LAVORATORI, 54-20029 CINISELLO BALSAMO, MI.. CARDIOLOGIA (ROME), (1986 (RECD 1987)) 31 (7), 539-544. CODEN: CARDDJ. Language: Italian.

AB The ability of antioxidants such as ubiquinone (UBI), .alpha.-tocopherol (Vit E) and superoxide dismutase (SOD) was examined in anesthetized rats in a model of coronary artery occlusion wiht subsequent reperfusion after 30 min or 5 min of myocardial ischemia. During reperfusion vulnerability

Searched by: Mary Hale 308-4258 CM-1 1E01

can increase and it was observed that it can be inversely proportional to the precedent ischemic injury. Ubiquinone and .alpha.-tocopherol administered ip (1 mg/kg) 1 hour before occlusion significnatly reduced ischemia-induced arrhythmias, mainly by decreasing the ventricular tachycardia incidence. On the more serious reperfusion-induced arrhythmias, after a mild ischemia (5 min), the effect of the 2 compounds was more evident and the mortality was significantly reduced (70% in control group and 20% in the 2 **treated** groups). MDA plasmatic levels were always decreased by **treatments** also after reperfusion. SOD was totally inactive. The lipophilicity, the antioxidant capacity and the membrane stabilization properties of ubiquinone and **vitamin E** can account for the reduced vulnerability of the cardiac **tissue** induced by **ischemia** and reperfusion.

L85 ANSWER 88 OF 93 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

86251371 EMBASE Document No.: 1986251371. Increased body fluid purine levels during hypotensive events. Evidence of ATP degradation. Woolliscroft J.O.; Fox I.H.. Department of Internal Medicine, Section of General Internal Medicine, University of Michigan, Ann Arbor, MI, United States. American Journal of Medicine 81/3 (472-478) 1986.
CODEN: AJMEAZ. Pub. Country: United States. Language: English.

AB **Tissue ischemia** leads to adenosine triphosphate (ATP) breakdown with elevation of body fluid ATP **metabolites**. This study tests the hypothesis that there is a direct relationship between periods of hypotension and body fluid uric acid and oxypurine levels in 19 prospectively studied patients. Significant elevations in urine oxypurine/creatinine clearance were found during periods of hypotension as compared with nonhypotensive periods ($p < 0.05$). During severe episodes of hypotension, the serum urate level was significantly elevated as well ($p < 0.05$). The increase in these body fluid products of ATP degradation may reflect cellular ischemia during hypotensive periods. There was a weak correlation ($r = -0.31$, $p < 0.001$) between the systolic blood pressure and urine oxypurine/creatinine clearance. However, variability in the appearance of body fluid ATP breakdown products during episodes of hypotension suggests the interplay of multiple factors in the degradation of ATP. The use of ATP degradation products to quantitate the physiologic significance of clinical events remains tantalizing but not proved.

L85 ANSWER 89 OF 93 CAPLUS COPYRIGHT 2003 ACS

1986:199846 Document No. 104:199846 Effects of intravenous glycerol on cerebral blood flow and tissue metabolism in acute cerebral ischemia in spontaneously hypertensive rats. Fujishima, Masatoshi; Ishitsuka, Takao; Yoshida, Fujio; Ibayashi, Setsuro; Shiokawa, Osamu; Sadoshima, Seizo (Fac. Med., Kyushu Univ., Fukuoka, Japan). Angiology, 37(2), 92-8 (English) 1986. CODEN: ANGIAB. ISSN: 0003-3197.

AB The effects of i.v. 10% glycerol [56-81-5] on cerebral blood flow (CBF) and metab. were studied in acute cerebral ischemia exptl. induced by bilateral carotid artery occlusion in spontaneously hypertensive rats (SHR). CBF was measured by the H clearance technique and brain tissue **metabolites** such as lactate [50-21-5], pyruvate [127-17-3] and ATP [56-65-5] in the ischemic brain frozen in situ were detd. by the enzymic method. In comparison with saline-infused SHR, the redn. of CBF in the thalamus following carotid occlusion was significantly small in the glycerol **treated** SHR. Supratentorial ATP concn. in the 3 h-ischemic brain was reduced in both groups of rats, but its redn. was significantly smaller in the glycerol-infused group than the other. Lactate and lactate-pyruvate ratio tended to be less increased in the glycerol rats, indicating that ischemic metab. was restrained by the **treatment**. I.v. glycerol is apparently effective against acute

Searched by: Mary Hale 308-4258 CM-1 1E01

cerebral ischemia from the view point of cerebral hemodynamics and metab.

L85 ANSWER 90 OF 93 MEDLINE
86245136 Document Number: 86245136. PubMed ID: 3836012. Lipid hydrolysis and peroxidation in injured spinal cord: partial protection with methylprednisolone or **vitamin E** and selenium. Anderson D K; Saunders R D; Demediuk P; Dugan L L; Braughler J M; Hall E D; Means E D; Horrocks L A. CENTRAL NERVOUS SYSTEM TRAUMA, (1985 Winter) 2 (4) 257-67. Journal code: 8501356. ISSN: 0737-5999. Pub. country: United States. Language: English.

AB Compression trauma of the cat spinal cord induces a very rapid alteration in the lipid metabolism of cellular membranes, including lipid hydrolysis with release of fatty acids including arachidonate, production of biologically active eicosanoids, and loss of cholesterol. This disturbance of cellular membranes can directly damage cells and can lead to the secondary development of **tissue** ionic imbalance, **ischemia**, edema, and inflammation with neuronophagia. Pretreatment with either the synthetic glucocorticoid methylprednisolone sodium succinate (MPSS) or the antioxidants **vitamin E** and selenium (Se) completely **prevented** the loss of cholesterol and partially inhibited lipolysis and prostanoid production. **Treatment** with MPSS significantly reduced the postinjury tissue necrosis and paralysis. Preliminary evidence indicates that pretreatment with **vitamin E** and Se also protected against the effects of spinal cord injury (SCI). We speculate that the ability of these agents to preserve function after SCI may, in part, reside in their capacity to limit the trauma-induced changes in lipid metabolism.

L85 ANSWER 91 OF 93 MEDLINE DUPLICATE 27
84114466 Document Number: 84114466. PubMed ID: 6420544. Role of leukocytes in acute myocardial infarction in anesthetized dogs: relationship to myocardial salvage by anti-inflammatory drugs. Mullane K M; Read N; Salmon J A; Moncada S. JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1984 Feb) 228 (2) 510-22. Journal code: 0376362. ISSN: 0022-3565. Pub. country: United States. Language: English.

AB The invasion of leukocytes into and around a myocardial infarct was studied in chloralose-anesthetized dogs subjected to 1-hr occlusion of the left anterior descending coronary artery and reperfused for periods up to 5 hr. Polymorphonuclear leukocytes adhering to the endothelium of blood vessels within the ischemic area are evident at the end of the occlusion period. During reperfusion, the leukocytes migrate into the myocardium and large groups of cells can be observed "streaming" toward the irreversibly damaged area after 5 hr reperfusion. Infarcted tissue produces 10 times more 12-hydroxyeicosatetraenoic acid (a metabolite attributed to the invading leukocytes) from arachidonic acid than adjacent "normal" areas of the ventricle. BW755C (10 mg/kg-1 i.v.), which inhibits both the lipoxygenase and cyclooxygenase pathways of arachidonic metabolism, attenuates leukocyte infiltration into the infarcted myocardium, **prevents** 12-hydroxyeicosatetraenoic acid formation and significantly reduces infarct size (P less than .005). BW755C also significantly diminishes the incidence of cardiac arrhythmias during infarction. In animals where circulating white cells are reduced 60% by **treatment** with hydroxyurea (20 mg/kg-1 i.v./day for 5 days), there is also a smaller infarct (P less than .01). Indomethacin (5 mg/kg-1 i.v.) and dexamethasone (0.2 mg/kg-1 i.v.), which do not affect leukocyte migration into the ischemic myocardium, do not reduce infarct size. It is proposed that migrating leukocytes contribute to the **tissue** injury accompanying myocardial **ischemia**, possibly by the release of proinflammatory mediators such as lipoxygenase products, free radicals (oxygen **metabolites**) and hydrolytic enzymes. Drugs which reduce

Searched by: Mary Hale 308-4258 CM-1 1E01

the migration and/or activation of leukocytes may be useful in reducing infarct size.

L85 ANSWER 92 OF 93 MEDLINE
83173685 Document Number: 83173685. PubMed ID: 6836966. [Effect of alpha-tocopherol on the hydroxylating system and lipid peroxidation in membranes of endoplasmic reticulum from ischemic rat liver]. Vliianie alpha-tokoferola na gidroksiliruiushchuiu sistemu i perekisnoe okislenie lipidov membran endoplazmaticheskogo retikuluma ishemizirovannoi pecheni krys. Voronov G G; Lukienko P I. VOPROSY MEDITSINSKOI KHIMII, (1983 Jan-Feb) 29 (1) 90-4. Journal code: 0416601. ISSN: 0042-8809. Pub. country: USSR. Language: Russian.
AB If 60 min long **ischemia** of a liver **tissue** lobe occurred after feeding of rats with oil emulsion of alpha-tocopherol at a dose of 50 mg/kg within 12 hrs during 2 days, the "ischemic" decrease in metabolism of amidopyrine and aniline, in content of cytochrome P-450 and activity of initial and middle steps of NADPH-dependent redox chain as well as intensification of ascorbate-dependent peroxidation of membrane lipids were **prevented** in endoplasmic reticulum of hepatocytes. The protective effect of alpha-tocopherol on these xenobiotics metabolism is apparently related to an increase in catalytic activity of cytochrome P-450, to the enzyme antioxidant and membrane-stabilizing properties.

L85 ANSWER 93 OF 93 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
77048758 EMBASE Document No.: 1977048758. Lysosomal mechanisms in production of **tissue** damage during myocardial **ischemia** and the effects of **treatment** with steroids. Fox A.C.; Hoffstein S.; Weissmann G.. Dept. Med., New York Univ. Sch. Med., New York, N.Y. 10016, United States. American Heart Journal 91/3 (394-397) 1976. CODEN: AHJOA2. Language: English.
AB Mortality from acute myocardial infarction has decreased by prompt detection and **treatment** of arrhythmias and it is now important to evaluate interventions which might decrease damage to the acutely ischemic or jeopardized myocardium. In general, these include hemodynamic interventions which improve myocardial blood flow or decrease metabolic demands, and biochemical interventions which augment anerobic metabolism, facilitate the flux of substrates and **metabolites**, or decrease early structural damage. The last category was investigated. By a combined ultrastructural and biochemical study using an experimental model of myocardial infarction, it was demonstrated that a correlation exists between lysosomal disruption and early cell damage, with posible amelioration by early **treatment** with pharmacologic doses of methylprednisolone.

(FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, JICST-EPLUS, WPIDS' ENTERED AT 10:07:12 ON 10 JUL 2003)
TOTAL FOR ALL FILES
L63 2864 S (L1 OR ISCHEMIA)(3A)TISSUE AND (TREAT? OR THERAP? OR PROPHYLA
L64 40 FILE MEDLINE
L65 38 FILE CAPLUS
L66 23 FILE BIOSIS
L67 30 FILE EMBASE
L68 5 FILE JICST-EPLUS
L69 10 FILE WPIDS
TOTAL FOR ALL FILES
L70 146 S L63 AND (VITAMIN E OR L2 OR L3 OR L4 OR (BETA OR DELTA OR GAM
L71 1 FILE MEDLINE

Searched by: Mary Hale 308-4258 CM-1 1E01

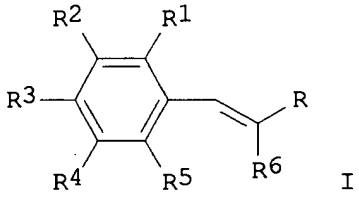
```
L72             6 FILE CAPLUS
L73             1 FILE BIOSIS
L74             1 FILE EMBASE
L75             0 FILE JICST-EPLUS
L76             1 FILE WPIDS
     TOTAL FOR ALL FILES
L77            10 S L63 AND (DAIDZEIN OR HESPERETIN OR LUTEOLIN OR TETRAHYDROXYFL
L78            40 FILE MEDLINE
L79            38 FILE CAPLUS
L80            23 FILE BIOSIS
L81            30 FILE EMBASE
L82             5 FILE JICST-EPLUS
L83            10 FILE WPIDS
     TOTAL FOR ALL FILES
L84           146 S L70 OR L77
L85            93 DUP REM L84 (53 DUPLICATES REMOVED)

=> s miller g?/au,in;s brown l?/au,in
'IN' IS NOT A VALID FIELD CODE
L86         2522 FILE MEDLINE
L87         3299 FILE CAPLUS
L88         3124 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L89         1758 FILE EMBASE
L90           11 FILE JICST-EPLUS
L91          812 FILE WPIDS

TOTAL FOR ALL FILES
L92        11526 MILLER G?/AU,IN


'IN' IS NOT A VALID FIELD CODE
L93         2407 FILE MEDLINE
L94         2769 FILE CAPLUS
L95         3031 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L96         1729 FILE EMBASE
L97           18 FILE JICST-EPLUS
L98          360 FILE WPIDS

TOTAL FOR ALL FILES
L99        10314 BROWN L?/AU,IN

=> s l92 and l99
L100            0 FILE MEDLINE
L101            6 FILE CAPLUS
L102            3 FILE BIOSIS
L103            0 FILE EMBASE
L104            0 FILE JICST-EPLUS
L105            5 FILE WPIDS

TOTAL FOR ALL FILES
L106           14 L92 AND L99

=> dup rem l106
PROCESSING COMPLETED FOR L106
L107            7 DUP REM L106 (7 DUPLICATES REMOVED)

=> d 1-7 cbib abs


Searched by: Mary Hale 308-4258 CM-1 1E01
```

L107 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
2003:154145 Document No. 138:198608 Tocopherol enriched compositions and amelioration of inflammatory symptoms. Beinlich, Peggy; Boddupalli, Sekhar; **Brown, Lesley**; Dreon, Darlene M.; Flaim, Stephen; **Miller, Guy**; Phinney, Stephen Dodge (Galileo Laboratories, Inc., USA). PCT Int. Appl. WO 2003015494 A2 20030227, 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US26920 20020821. PRIORITY: US 2001-PV314257 20010821; US 2001-PV314223 20010821; US 2001-PV314256 20010821.

AB The present invention provides non-alpha-tocopherol enriched tocopherol compns. and non-alpha-tocopherol metabolite enriched compns. for use in the redn. of inflammatory markers assocd. with inflammation and for use in the treatment and/or amelioration of symptoms of inflammation assocd. with for example, cardiovascular diseases or disorders, infectious diseases, diabetes, SIRS, asthma, neurodegenerative disorders, PMS; muscle fatigue or inflammation; and dermal conditions. Effects of tocopherols on inflammatory mediators was studied in adults with end-stage renal disease.

L107 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
2003:97274 Document No. 138:153318 Preparation of substituted phenols as cytoprotective agents useful in pharmaceutical and cosmetic formulations. Wang, Bing; Zhang, Yong-Kang; Chen, Jian; Zhang, Wei; Song, Jiangao; Del, Balzo Ughetta; **Brown, Lesley; Miller, Guy** (Galileo Laboratories, Inc., USA). PCT Int. Appl. WO 2003009807 A2 20030206, 161 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US23509 20020723. PRIORITY: US 2001-PV307439 20010723; US 2002-PV353702 20020131.

GI



I

AB Phenolic derivs. having conjugated bonds I [wherein R = NO2, substituted alkenyl, or (un)substituted aryl(carbonyl), heteroaryl, or heterocyclyl; R1-R5 = independently H, carboxy, CN, halo, OH, NO2, nitrone, sulfonate, or (un)substituted alkoxy(carbonyl), alkenyl, alkyl, or (hetero)aryl; or 2 adjacent members of R1 to R5 = O- and together complex with C or a metal; provided that at least 1 of R1 to R5 = MeOCH2O or H(CH2CMe=CHCH2)n; n =

Searched by: Mary Hale 308-4258 CM-1 1E01

1-4; further provided that when R1 to R5 = MeOCH2O, R = Ph para-substituted by CN, NO2, nitroso, NHOH, NH2CO, alkyl ester, N-contg. heterocyclyl, etc.; R6 = H or (un)substituted alkoxycarbonyl; or stereoisomers or pharmaceutically acceptable salts thereof] were prepd. as cytoprotective agents useful in pharmaceutical and cosmetic formulations. For example, coupling of (4-nitrobenzyl)triphenylphosphonium bromide with 3,4-bis(methoxymethoxy)benzaldehyde using LiOEt in EtOH (41%) followed by deetherification with concd. HCl in EtOH gave 4-[2-(4-nitrophenyl)vinyl]benzene-1,2-diol (81%). The latter was among invention compds. that showed significant redn. in edema in assays assessing rat paw edema (10 to 70%, $p < 0.05$) and mouse ear inflammatory response to topical arachidonic acid (15 to 80%, $p < 0.05$). Results from the neuronal cell stress assay and the rat middle cerebral artery occlusion model of cerebral ischemia were also disclosed for selected invention compds. Thus, I are useful in the treatment of certain ischemic or inflammatory conditions, including but not limited to stroke, myocardial infarction, congestive heart failure, and skin disorders characterized by inflammation or oxidative damage.

L107 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
2003:169981 Document No. 138:180774 Compositions of flavonoids and synergists for use as cytoprotectants and methods of making and using them. **Brown, Lesley A.**; Miller, Guy (Galileo Laboratories, Inc., USA). U.S. US 6528042 B1 20030304, 28 pp. (English). CODEN: USXXAM. APPLICATION: US 2000-684607 20001006. PRIORITY: US 1999-PV159003 19991008.

AB Non-naturally-occurring compns. for use in amelioration of disruption of energy metab. secondary to stress are described. These compns. comprise a flavonoid or deriv. thereof and a synergist. Synergists include, but are not limited to, amino acids, carbohydrates, carnitines, flavonoids, nucleosides, and tocopherols and/or derivs. thereof. Methods of making these compns. and methods of ameliorating disruption of energy metab. secondary to stress, comprising administering such synergistic compns., are also disclosed.

L107 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 4
2002:927398 Document No. 138:19518 Sponge-derived terpenoids and their synthetic derivs. uses in treatment of lipoxygenase-mediated inflammatory conditions. Crews, Phillip; Carroll, Jennifer; **Miller, Guy**; Bobzin, Steve; **Brown, Lesley**; Holman, Theodore (The Regents of the University of California, USA). PCT Int. Appl. WO 2002096870 A2 20021205, 70 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US17171 20020531. PRIORITY: US 2001-PV295258 20010531.

AB Compds. that are effective lipoxygenase inhibitors, and methods and pharmaceutical compns. for inhibiting lipoxygenases and for treatment of lipoxygenase-mediated conditions in humans and other subjects. The compds., methods and pharmaceutical compns. utilize subersic terpenoids, jaspic terpenoids, igernellic terpenoids, hippospongic terpenoids, halicondric terpenoids, dictyodendric terpenoids, and/or heteronemic terpenoids, and synthetic derivs. or analogs thereof. Exemplary compds. include (-)-subersic acid, (+)-subersin, jaspaquinol, (-)-jaspic acid, igernellin, halisufate 7, and hipposulfate C and D, and derivs. thereof.

Searched by: Mary Hale 308-4258 CM-1 1E01

#6 = inventive utility

L107 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 5
2002:465811 Document No. 137:28330 Compositions and methods for the treatment of tissue ischemia. **Miller, Guy Michael**; Brown, Lesley A.; Del Balzo, Ughetta; Flaim, Stephen; Boddupalli, Sekhar; Wang, Bing (Galileo Laboratories, Inc., USA). PCT Int. Appl. WO 2002047680 A2 20020620, 130 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US50984 20011214. PRIORITY: US 2000-PV256269 20001215; US 2001-PV296581 20010606; US 2001-PV296580 20010606; US 2001-PV343575 20011019.

AB The present invention provides compns. and methods for the treatment of tissue ischemia, and in particular, cerebral ischemia. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compns. and gamma-, beta, or delta-tocopherol metabolite enriched compns. and/or flavonoid enriched and/or a flavonoid deriv. enriched compns. and methods for their use in preventing or treating a tissue ischemic condition or a cerebral ischemic condition. The present invention also provides pharmaceutical compns. comprising gamma-, beta-, or delta-tocopherol enriched tocopherol compn., a gamma-, beta-, or delta-tocopherol metabolite enriched compns. or flavonoid enriched compns. or flavonoid deriv. enriched compns.

L107 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 6
2002:570708 Document No. 137:119700 Formulations of tocopherols and methods of making and using them. **Miller, Guy**; Brown, Lesley A. (Galileo Laboratories, Inc., USA). U.S. US 6426362 B1 20020730, 28 pp. (English). CODEN: USXXAM. APPLICATION: US 2000-684588 20001006. PRIORITY: US 1999-PV158234 19991008.

AB Non-naturally-occurring compns. for use in amelioration of disruption of energy metab. secondary to stress are described. The compns. comprise a tocopherol and/or a deriv. thereof, and a synergist, and are particularly suited for use as nutritional supplements. Synergists include, but are not limited to, flavonoids and lactoferrin and/or derivs. thereof. Compns. comprising an optimized formulation comprising a tocopherol and an addnl. compd. such as daidzein or biochanin A are also described. Methods of making these compns. and methods of ameliorating injury(ies) or disruption of energy metab. secondary to stress, comprising administering such compns., are also disclosed. Various concns. of tocopherols and flavonoids were tested in vitro for the combined ability to ameliorate disruption of energy metab. secondary to stress. For example, diosmin (3.3-100 .mu.M) was not protective by itself, but was synergistic in that range with 10 .mu.g/mL (.+-.)-.alpha.-tocopherol, a concn. at which (.+-.)-.alpha.-tocopherol was only slightly (about 15%) protective by itself. The combination of 100 .mu.M diosmin and 100 .mu.g/mL (.+-.)-.alpha.-tocopherol greatly reduced cell death, providing about 70% protection against stress-induced cell death, indicating synergism between these components. A combinations of 100 .mu.M diosmin and 11 .mu.g/mL (.+-.)-.alpha.-tocopherol was also synergistic.

L107 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2001:279990 Document No.: PREV200100279990. Dereplication and evaluation of redox bioactive phytonutrients derived from food sources. Boddupalli, Sekhar S. (1); **Brown, Lesley (1)**; Loftus, Megan (1); Flaim,

Searched by: Mary Hale 308-4258 CM-1 1E01

Stephen (1); **Miller, Guy (1)**. (1) Galileo Laboratories Inc, 5301 Patrick Henry Dr, Santa Clara, CA, 95054 USA. FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A287. print. Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001 ISSN: 0892-6638. Language: English. Summary Language: English.

AB Recent reports suggest that diets high in citrus can significantly reduce the incidence of stroke and cardiovascular diseases. Many dietary phytonutrients have been shown in recent years to be protective against oxidative stress and inflammation. In the light of the potential impact of these compounds on human health it is important to elucidate the specific beneficial and detrimental interactions among bioactives, and the mechanisms involved. The ability of these phytonutrients and their natural mixtures to block the cellular injury against oxidative stress and their effects on the protection induced upon inflammatory challenges was investigated. Various citrus and grape fruit extracts as well as the specific pure flavonoids that are the major constituents in these fruit sources were taken through bioassay directed fractionation using cell lines that are energetically and metabolically competent. Specific flavonoids showed dose dependent down-regulation of protein expression induced by an inflammatory challenge. However, whole extracts containing the same flavonoids as their major constituents did not possess as potent an anti-inflammatory activity. Similar results were obtained when the flavonoids and extracts were tested for protection of cells against oxidative damage. Based on the above data, the following may be generally concluded; (i) complex phytonutrient mixtures can act at multiple targets to produce an aggregate beneficial or detrimental response; (ii) the net biologic response can be attenuated through weak agonist competitive antagonism.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	455.02	564.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-18.88	-18.88

STN INTERNATIONAL LOGOFF AT 10:31:29 ON 10 JUL 2003

Searched by: Mary Hale 308-4258 CM-1 1E01